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The Chemotherapy of Surra (Trypanosoma evansi Infections) of Horses and Cattle in India

BY

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CONTENTS

THE CHEMOTHERAPY OF SURRA (*TRYPANOSOMA EVANSI* INFECTIONS) OF HORSES AND CATTLE IN INDIA.

BY

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(*Received for publication on 25th September 1926.*)

I. Introduction.

The experiments described in this paper were planned in order to discover an effective, cheap, and easily applicable system of treatment for surra for adoption in the field. Work in this direction was commenced in 1922 and is still in progress, and hence the deductions drawn from the observations hitherto made are to some extent provisional.[1] Early in the course of the investigation supplies of the cheaper trypanocidal agents, such as the relatively simpler compounds of arsenic and bismuth, were procured for test, as it was thought that the desired quality of efficacy in treatment might be attained by a suitable alternation in the application of such materials, to overcome the known tendency on the part of the parasites towards the development of " drug-fastness " against individual agents, while at the same time the desideratum of cheapness essential in evolving systems of treatment for animal subjects would also be secured. Likewise, on account of the known extremely high susceptibility of the equine species to surra and the unsatisfactory results obtainable from the systems of therapy already devised for the treatment of infection in this species, researches were commenced using the considerably more resistant bovine species as test subjects. A strain of trypanosomes recovered from a natural outbreak of surra among buffaloes at Muktesar proved eminently suitable for use in these tests, but unfortunately, early in 1924, the strain lost its virulence and strenuous endeavours to exalt it and other strains by passage through cattle proved fruitless. While the strain retained its high virulency for cattle it invariably produced death in control animals in a few days and thus useful knowledge was readily obtainable regarding the materials effective in the treatment of these animals. As will be stated later, however, the information forthcoming from the results of experimental therapy in the bovine species did not furnish exhaustive guidance as to the systems likely to be effective with the equine species, for, briefly,

[1] The experimental animals reported to have shown all the appearances of recovery at the time of the preparation of the original draft of this paper, early in 1926, have since progressed in bodily condition and shown no indication of relapse, at the date of the submission of the final proofs, n November 1927. The writer is therefore sanguine that the work recorded in this Memoir has eventually achieved, in very large measure, the objects which he set out to resolve.

clinical " cures " could be readily obtained with the use of relatively simple treatment in the face of virulent infection in the bovine species, as such " cures " did not necessitate complete sterilization of the tissues of trypanosomes, which condition appears to be essential for the continued obliteration of morbidity in the equine species. It was not until the middle of 1925, when supplies of the preparation known as " Bayer 205 " were kindly forwarded for trial by the manufacturers, that experimentation with the equine species was considered, after preliminary trials, to be economically justifiable, and thereafter, subsequent to a number of what may be termed qualitative trials in the field of therapy with the equine species, it was considered that investigations might be profitably resolved into and confined to certain definite simple channels, involving the use of this therapeutic agent.

In the trials briefly discussed now in this paper the drugs employed were :— (1) " Bayer 205," samples of which were forwarded by the Bayer firm (Farbenfabriken vorn Friedr. Bayer & Co., Landwirtschaftliche Abteilung, Leverküsen, Germany) who, in compliance with their wishes, were kept informed of the general progress of the experiments ; (2) tryparsamide, supplies of which were obtained early in the course of the investigations through the courtesy of Dr. Louise PEARCE of the Rockefeller Institute for Medical Research, New York, U. S. A. ; (3) tartar emetic ; and (4) bismuth compounds, represented by the insoluble bismuth phosphate and the soluble bismuth sodium tartrate.

In addition to the experimental work carried out at the Muktesar laboratory, a certain amount of research was performed in collaboration with veterinary colleagues in the field in India belonging to both the Army and Civil Departments. In this connection the author wishes to mention especially the researches carried out by Mr. T. F. QUIRKE, Chief Superintendent, Civil Veterinary Department, Punjab, and his staff, at the Sohawa laboratory and elsewhere. The reports forthcoming from the field workers are not dwelt upon in this paper, except in so far as the experiences communicated by them lend substantial support to the observations made under more precise circumstances at the Muktesar laboratory.

The horses used in the experiments were for the most part cast army horses kindly supplied to the laboratory by the Army authorities in India for experiment. In addition, groups of ponies and donkeys were purchased, specially for certain tests.

The strains of trypanosomes used in the experiments upon the equine subjects at Muktesar particularly the one designated under the name of " Peora " strain (see charts of Ponies 81, 82 and 83), were generally highly virulent, and invariably proved fatal when inoculated into control subjects, the average incubation period of the disease (that is, until the time of appearance of trypanosomes in the peripheral blood) being 5 to 6 days. The virulent bovine strain used in the early experiments behaved in a similar manner towards cattle. Observations on the incubation period of the disease in 22 horses, with the details of the strains employed, are summarized in Table I.

It will be observed from the table that a number of equines were inoculated with virulent blood intrathecally. The inoculation of virulent blood by the intrathecal route was relatively simple in the case of horses, but in the earlier experiments inoculation of donkeys in this manner proved fatal in certain instances, apparently owing to excessive laceration of the meninges caused by repeated redirection of the needle, since *post-mortem* examination in such cases showed the presence of extravasated blood along the needle track in the muscles over the occipito-atlantal space, hæmorrhagic deposits over the spinal cord near the seat of puncture, and blood-tinged cerebro-spinal fluid, although the cord itself presented no macroscopical lesions. Use was made of the indications thus furnished by the results of *post-mortem* examination, and no further accident occurred during subsequent operations. The technique of intrathecal punctures as now employed is described later.

As will be seen from the table, no difference in the intensity of the infection was observable, whether the intrathecal or subcutaneous route was employed for the purpose of infective inoculation. However, the fact that the trypanosomes, although carefully introduced into the spinal canal, invariably made their way, shortly afterwards, into the blood stream would appear to be of significance in the elucidation of the genesis of relapse strains, and recalls similar results obtained by REICHENOW (1914), who injected infected human blood into the spinal canal of a monkey and found trypanosomes in its blood 21 days later.

The examination of cerebro-spinal fluid, obtained by means of lumbar puncture with a view to determining the cell content, constitutes one of the most important items in the routine procedure connected with the treatment of human sleeping sickness. The method would, however, appear to have found little application in the experimental therapy of animal trypanosomiasis, in which the results of the examination of blood smears are regarded usually as a sufficient indication of the extent to which amelioration has been effected by a certain course of treatment; the results of blood examination are enhanced in accuracy by ascertaining the effect of the inoculation of a quantity of the circulating blood into a very susceptible species. In the present series of experiments, however, death occurred in a number of instances in which the trypanosomes, although absent in the peripheral circulation, were detected in large numbers in centrifuged cerebro-spinal fluid, so that the animals evidently succumbed as the result of injuries caused to the central nervous system. The periodical examination of the cerebro-spinal fluid was, therefore, undertaken in some of the experimental subjects, and the character of the cell content was noted whenever indications were obtainable of a deviation from the normal, as evidenced by the occurrence of leucocytosis and the presence of "mulberry cells." (See Figs. 1 and 2 illustrating the method of withdrawing cerebro-spinal fluid.)

Surra.—General Remarks upon the Disease.

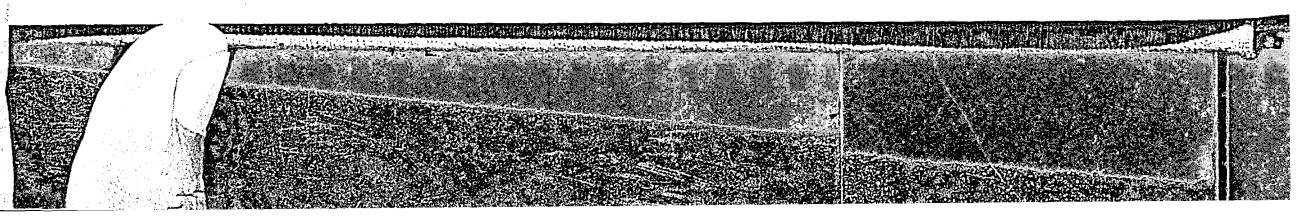
The term *surra*—a Hindi word meaning "rotten"—is used collectively to designate the disease condition produced in animals in India by the protozoan organism *Trypanosoma evansi*, which was discovered as early as in the year 1880

by Griffith Evans in the blood of camels. The disease appears to have a somewhat widespread distribution in the East and Near East. It occurs in Eastern and Western India and also in the adjoining Chinese territories, and has been established, during comparatively recent years, in the Malayan and Philippine Islands, Sumatra, Java and Mauritius, and in the last named country the disease is believed to have been introduced with cattle imported from India. The condition affecting notably camels in Northern Africa and known as "debab" is probably identical; it is not unlikely that certain trypanosomiases in Central America (caused by the trypanosomes designated as *T. venezuelense* and *T. hippicum*) are also very closely related. In natural circumstances infection occurs in equines, camels, cattle (including buffaloes), dogs, and elephants.

The causal organism presents considerable resemblance to *Trypanosoma brucei*, which similarly affects animals in Africa, with the disease known as nagana, but as seen in smears of blood from infected animals in India, *T. evansi* is invariably monomorphic, and no suggestion of polymorphism, which frequently characterizes certain strains of *T. brucei*, has hitherto been recorded in connection with it. This observation may be of some importance in connection with the question of natural transmission if we accept the purport of the recently recorded researches of Duke, that polymorphism is somehow connected with cyclical transmission in an insect vector. The organism has been proved to be mechanically transmitted by *Tabanus striatus* (Mitzmain; Shilston and Patel) and by *Tabanus albimedius* (Cross and Abdulla Khan, 1924). In 1921, Cross and Patel published results to prove that infection was cyclically transmitted by the tick, *Ornithodorus crossi*, but Yorke and Macfie (1924), in Liverpool, repeated the experiments with infected ticks with negative results.

Horses, donkeys, and mules are most susceptible to surra. In these animals, after artificial infection with the disease, the period of incubation ranges from about four days to a fortnight, and is followed by a rise of temperature and the appearance of trypanosomes in the blood stream. A marked increase of trypanosomes occurs periodically in the blood in the course of the disease accompanied by a corresponding elevation of temperature, with intervening periods of abatement. Petechiæ soon develop on the mucous membranes, particularly on the conjunctivæ, followed by the appearance of œdematous swellings of various degrees of severity in the extremities and dependent parts (sheath, belly, breast) and urticarial eruptions, often transitory in appearance, on the skin. As the disease advances, there is progressive discoloration of the mucous membranes, and although the appetite generally continues unimpaired, or with appreciable diminution during the febrile crises, the animal becomes greatly emaciated, and develops paralysis of the hind quarters, and succumbs, usually within a period of two months after the first appearance of the trypanosomes. In equines the disease almost invariably progresses to a fatal issue.

Indigenous cattle in India are often stated to be immune to surra, but to be capable of acting as "reservoirs" of the trypanosomes. Indeed, native cattle,



including buffaloes, are extremely commonly found to carry the trypanosomes in a latent state of activity without displaying any manifest symptoms of ill-health. This phenomenon has been frequently brought to our notice in the course of blood examinations executed in the course of the routine processes for the manufacture of anti-rinderpest serum, and systematic examinations of infected buffaloes over several months would seem to indicate that trypanosomes persist in the tissues of the animals, relapsing in relatively small numbers at relatively prolonged intervals in the blood stream, for a long time, and may probably persist in this manner during the whole lifetime of the animals. It would seem also that a concomitant attack of rinderpest is capable of accentuating markedly the relapse of the trypanosomes. Not infrequently, however, virulent outbreaks of surra occur among cattle, and notably among buffaloes, in which a mortality rate amounting to 25 or 30 per cent. of the buffaloes in a locality supervenes, and some outbreaks have been reported with still higher mortality, 75 to 85 per cent. We have had experience of such virulent outbreaks during the course of these investigations among the buffaloes maintained for serum production at Muktesar, and have been able to obtain valuable information in regard to treatment in the course of these outbreaks. As has been mentioned elsewhere in this paper, the tissues of the bovine animals seem capable of responding readily to the extent of keeping down the rate of multiplication of the trypanosomes to the status of relatively innocuous invaders, so that, after an initial intervention with a simple chemotherapeutic agent to stay the progress of a virulent attack, the animal's tissues are able of their own accord to suppress further dangerous multiplication of the parasites. Considering that bovine trypanosomiasis has such a widespread distribution in India, it is a point that cannot fail to excite curiosity as to why the equine affection is not more common than it is, having in mind that naturally acquired surra spreads rather rapidly among horses, when cases commence to appear in these animals.

According to Cross (1922), who has made a special study of the disease in camels in India, surra occurs in camels in both acute and chronic forms. The acute form is generally encountered in animals of very advanced age and they die within periods varying from a few weeks to a few months, a characteristic feature of such cases being the almost continuous presence of trypanosomes in the peripheral circulation, accompanied with fever. The acute form may also be characterized by the occurrence of pronounced cerebro-spinal symptoms, and in such cases the onset of death is sudden, the camel frequently bolting or falling down in a convulsion. In the chronic form, the course of the disease extends from two to five years ; the animals become greatly emaciated and develop paralysis of the limbs and die with symptoms of severe anæmia.

Outbreaks of surra are not uncommon in dogs in India, and the affection would appear to pursue usually an acute course, somewhat resembling that observed in equines.

The gradation of the pathological pictures presented by infection in the different classes of domesticated animals in India is thus a phenomenon of considerable interest. Likewise, the varying resistance presented strikingly by individuals of one class, such as the camel, is suggestive of the favourable part played by good physical condition in attenuating morbidity following upon infection.

The Chemotherapy of Trypanosomiasis, with especial Reference to Surra.

It may not be irrelevant to set forth the principles of this class of investigation at this stage. Chemotherapy as a scientific study, claiming a status more or less distinctly marked off from the science of general pharmacology, owes its origin to the imaginative genius of Paul EHRLICH who, from the results of his researches upon the biological properties of dye-stuffs, was the earliest to recognize the possibilities of therapeutic investigations directed with the object of evolving substances which, to use EHRLICH's own terminology, would be "maximally parasitotropic" and "minimally organotropic." Chemotherapy thus differs from general pharmacology in its greater precision; in short, it may be regarded as pharmacology redeemed from empiricism.

It must be owned, however, that in the history of traditional pharmacology much has been achieved by means of intelligent empiricism and schemes of curative treatment have been formulated which have been none the less successful by reason of a lack of that logical rigour which imparts to the science of chemotherapy its distinctive value.

While to EHRLICH must be credited the first genuine attempt thus to rationalize conventional pharmacology by directing attention to the parasites themselves instead of the diseases caused by them, subsequent researches have indicated that EHRLICH's theory of "distribution" was much too simple to account for the complex phenomena arising out of the interaction of the host and the parasite on the one hand and the chemotherapeutic agent on the other, and during recent years there has accumulated a vast amount of literature setting forth rival theories to explain the mechanism of the chemotherapeutic reaction. As DALE (1923) observed in regard to EHRLICH's "distribution" theory, "The knowledge yet available concerning the chemistry of the protoplasm has no point of contact with a conception of this kind. Such knowledge affords no suggestion as to the nature of the chemical differences between the protoplasm of the vertebrate and that of the unicellular parasite and furnishes no basis for prediction, or even for surmise, with regard to their differential affinities for chemical substances of known constitution."

In spite of all that has been admirably set forth by DALE, it is an interesting commentary on the validity of EHRLICH's original conceptions that one notices in much of what has been published during very recent years unmistakable evidence of a tendency to drift back to the basic assumption of preferential affinity, as originally enunciated by EHRLICH. As a matter of fact, much of the modern science

of chemotherapy would appear to need rescuing from the rigour of sophisticated logic, in order that chemotherapeutic endeavours may be directed, unburdened with platitudes, into channels of investigation calculated to yield results of that practical value which constituted the saving grace of orthodox pharmacology.

In the following outline of the experimental therapy of trypanosomiasis, no attempt will be made to indicate even by reference, the whole of the enormous wealth of recorded observations concerning the curative and prophylactic value of particular drugs that have been introduced from time to time into the field of investigation. The aim will be, on the other hand, to sketch very briefly the general course of progress along three well-recognized routes of research, noting in particular the extent of success that has attended chemotherapeutic endeavours in the treatment of the disease condition known as surra.

(i) *Treatment with dyes and analogous compounds.* The idea of employing the aniline dyes as curative agents in the treatment of parasitic infections first suggested itself to EHRLICH in 1891, as the result of observations made in collaboration with GUTTMAN on the staining of the malaria parasite with methylene blue. A considerable number of dyes and related compounds (*e.g.*, trypanred, trypanblue, afridol violet, parafuchsin, tryparosan, trypaflavin, acridin) have since been introduced into the field of chemotherapeutic investigation and the circumstances attending the discovery of certain of them constitute interesting chapters in the evolutionary history of the science of chemotherapy. These drugs have, however, proved of little practical value in the treatment of trypanosome infections and the investigation of further compounds of this class had been almost abandoned until the advent of "Bayer 205," which, at the present time, bids fair to capture the entire field of the experimental therapy of trypanosomiasis. Details concerning the extent to which the drug has proved of value in the treatment of trypanosomiasis will be discussed at relevant points later in this paper.

(ii) *Treatment with compounds of arsenic.* Since BRUCE (1897) and LINGARD (1899) first used arsenic in the treatment of animal trypanosomiasis, a considerable number of arsenical compounds, almost bewildering in the variety of their chemical configuration, have been introduced into the field of experimental therapy and the details available concerning their efficacy constitute by far the largest chapter in the history of chemotherapeutic endeavour.

In the long list of arsenical derivatives, premier place must be accorded to atoxyl as being the drug which, from the date of its early introduction by THOMAS and BREINL (1905), right up to the present moment, has found extensive application in the treatment of human sleeping sickness, and has held its ground against such formidable rivals as "Bayer 205" and "tryparsamide"; even to this day French workers recommend "atoxylization" as the most effective and inexpensive measure of prophylaxis for adoption in the field.

The use of atoxyl as a remedy for surra appears to have been first made by LAVERAN and THIROUX (1908). These authors obtained encouraging results in

the case of five guinea-pigs treated with atoxyl alternated with orpiment orally administered in the form of pillules. Subsequently, THIROUX and TEPPAZ (1908, 1909) carried out extensive series of experiments on the efficacy of this combination in the treatment of horses and camels affected with surra and the results obtained were generally satisfactory. They found that camels bore orpiment badly, although they tolerated atoxyl much better than horses did.

FRASER and SYMONDS (1908), in the Federated Malay States, treated three horses, which included one Javanese pony and an Australian mare, with atoxyl, alone or in combination with mercuric chloride. All the animals died shortly after the commencement of the treatment. It would appear, however, that they did not show trypanosomes in their blood at the time of death.

HOLMES (1908), in India, tested the efficacy of the atoxyl-orpiment treatment for ponies, guinea-pigs, and rabbits experimentally infected with surra, and obtained variable results. In 1909 HOLMES gave an account of a series of experiments conducted with the object of confirming his earlier results and also of testing the effect of the treatment when commenced at an advanced stage of the disease. The conclusions arrived at by him were as follows :—

" The results of these experiments show that surra in rabbits and guinea-pigs can be cured by a few doses of atoxyl administered according to the method of LAVERAN and THIROUX.

" In ponies and horses the same treatment can effect a cure even in advanced cases, but it does not succeed in all cases and all animals cannot tolerate the drugs.

" A combination of tartar emetic, atoxyl and orpiment, and also a combination of atoxyl, orpiment and sodium arsenite can be used with success.

" In a series of experiments, the combination of atoxyl, sodium arsenite and orpiment has given results superior to any other treatment."

In a later paper, HOLMES (1910) discusses the relative efficacy of various arsenicals in the treatment of equine surra and refers to the superiority of arsenious acid over all other arsenicals, including atoxyl.

HOLMES (1913) also tested the efficacy of salvarsan, but the results do not appear to have been encouraging.

LAFONT (1910), in Mauritius, found, however, that arsenious acid used alone or associated with other arsenicals did not yield such results as had been obtained by HOLMES in India.

THIROUX and TEPPAZ (1910), in commenting upon the results obtained by HOLMES, emphasize the desirability of employing atoxyl with extreme prudence inasmuch as the sensibility of horses *vis-à-vis* the medicament is imperfectly known.

GAIGER (1909) records having successfully treated two cases of equine surra by the atoxyl-orpiment method, although he does not regard the method suitable for the treatment of surra in camels and dogs. In a later paper (1911) he stated that

" cure " was effected only in four out of a total of twenty-five cases of equine surra treated by means of arsenicals.

LISHMAN (1911) records a striking instance of the efficacy of soamin in the treatment of an advanced case of spontaneous equine surra.

LEESE (1910, 1912) records the results obtained in the treatment of camel surra by means of atoxyl combined with sodium arsenate and antimony tartrate and recommends what he describes as the " 668 method " as the best treatment for surra in camels.

WALKER (1914) tested the efficacy of a combination of arsenious acid and atoxyl in the treatment of four cases of equine surra, but the results were very disappointing.

CROSS (1914) carried out a series of experiments with the use of soamin, arsenious acid and tartar emetic upon camels infected with surra, particularly with the object of determining the relative value of instituting treatment when the trypanosomes were present or absent in the peripheral circulation and concluded that the treatment could be employed with equal advantage in both conditions.

Undoubtedly one of the most notable papers on the efficacy of arsenicals in the treatment of surra is that of STRONG and TEAGUE (1910). The drug employed by these authors was arsenophenylglycin (supplies of which were obtained from EHRLICH). Although " cure " was effected only in seven out of a total of 20 cases treated with the drug, the authors conclude: " We do not hesitate to say that arsenophenylglycin has proved to be by far the most satisfactory means of treatment yet discovered."

Perhaps the success of experimental research upon the efficacy of arsenicals can best be judged by the fact that their use finds no application in routine field treatment of surra in India at the present day.

(iii) *Treatment with compounds of antimony and bismuth.* According to DALE (1923), CUSHNY made the first suggestion of a trial of compounds of antimony and bismuth on account of their relationship with arsenic. LOW (1916), in the course of a review of the history of the use of tartar emetic in tropical medicine, states that NICOLLE and MESNIL (1906) first proposed the use of antimony salts in the treatment of trypanosomiasis.

The compounds of antimony that have been used as remedies for trypanosome infections are practically confined to two substances, namely, antimony trioxide, or trixidin, and potassium antimonyl tartrate, or tartar emetic. Trixidin would, however, appear to have had a very limited application, although, on account of the fact that it is the only compound of trivalent antimony possessing a low toxicity, it was regarded by KOLLE and collaborators (1914) as a drug of considerable promise. YORKE and BLACKLOCK (1914), however, found that when administered intramuscularly the drug was only slightly absorbed and when injected intravenously the drug was immediately deposited from the suspension.

Details concerning the value of tartar emetic and the salts of bismuth will be discussed at relevant points in the ensuing pages.

II. Treatment of Equine Surra with "Bayer 205."

Although "Bayer 205" was the drug introduced last into our experimental researches at Muktesar, and the observations upon its efficacy are still in progress, it will be convenient to discuss the results of treatment with it, first of all.

Considering the brief space of time that has elapsed since the introduction of the drug into the field of therapeutic investigation, the drug would appear to have found a remarkably wide application in the treatment of trypanosomiasis, whilst the laboratory experiments carried out with a view to exploring its therapeutic possibilities have been both varied and intensive.

Although the introduction of "Bayer 205" has thus registered a definite advance in the history of the experimental therapy of trypanosomiasis since Bruce's and Lingard's early employment of arsenic, the results recorded by various workers would appear to indicate that the drug is of very limited value in the treatment of certain forms of animal trypanosomiasis and in the advanced stages of human sleeping sickness. As Rodenwaldt (1923) observes, the results of experiments upon laboratory animals infected with dourine have sometimes been encouraging and the results thus obtained in Europe have at first also received confirmation in the hands of workers employed in the colonies, but relapses have occurred frequently at later periods and the animals have eventually succumbed. The relapses have been frequent and radical cures exceptional and obtained only in cases of recent infection when intervention has occurred shortly after the appearance of the first symptom. Rodenwaldt and Douwes (1922) point out that Haendel and Joetten, although attributing to "Bayer 205" curative properties when tested in laboratory conditions, are sceptical about its efficacy in the treatment of naturally contracted infection. Pfeiler, Miessner and Berger also found the drug efficacious for artificially induced dourine, but state that its action is uncertain when employed in natural conditions and that the parasites reappear after having been absent from the blood for two months. The statement with regard to the interval prior to reappearance of the trypanosomes is of importance in view of what has to be said later on this subject.

Van Saceghem (1924), in reviewing the results obtained with "Bayer 205" in the treatment of various forms of animal trypanosomiasis, observes that although the drug may favourably influence the course of dourine and mal de caderas, it is valueless against *T. vivax* and is of little value in the treatment of equine surra, whilst its curative effect in the case of *T. congolense* infection is only temporary.

It seems to us not improbable that the action of the drug may differ considerably with infections due to the several groups of pathogenic mammalian trypanosomes. Thus, while the recorded evidence would tend to show that the drug has at any rate a marked effect upon trypanosomiasis due to the *brucei* group, its action may be

only slight with infection due to trypanosomes of the other chief groups, the *vivax* group and the *congolense-dimorphon* group.[1]

Perhaps the most disappointing results as yet obtained with " Bayer 205 " are those recorded by RODENWALDT and DOUWES (1922). These authors found that the drug was not only valueless against equine surra but was definitely toxic for horses, whether administered in small or large doses. The observations of RODENWALDT and DOUWES must, however, be regarded as exceptional inasmuch as BAERMANN (1922), BUBBERMAN and collaborators (1925), BAKKER (1925) and BERG (1925) have all recorded what would appear to be generally encouraging results obtained by means of " Bayer 205 " employed alone or in combination with tartar emetic or atoxyl, in the treatment of equine surra. In view of these results it seemed desirable to explore the possibilities of the drug as a remedy for the disease condition as it occurs in India.

" Bayer 205," as originally issued by the Bayer firm, was described by HAENDEL and JOETTEN (1920) as a white, fine, flaky powder, slowly but completely soluble in cold water, to make a 10 per cent. solution, which was odourless, slightly bitter, and neutral in reaction; it kept well if protected from light and was sterilizable without undergoing alteration. On the other hand, the product used by BRUMPT and LAVIER (1922) was of a slightly " roseate tint and presented, in solution, an odour very distinctly recalling that of acetone products." Likewise, the drug, as employed by VAN SACEGHEM (1924), in the treatment of animal trypanosomiasis, was of a pink colour. The samples obtained by us conformed with this description.

The product, as at present issued by the Bayer firm, would appear to comprise two distinct " brands " designated under the names of " Bayer 205 " or " Germanin" and " Bayer 205 (Vet.) " or " Naganol," for human and veterinary use, respectively. Without attempting to enter into the profundity of the chemical configuration of " Bayer 205 "[2], the honest clinician, in the absence of assurance from the Bayer firm to the contrary, may perhaps pertinently be led to regard the two " brands "

[1] This belief would appear to be supported by what has been recorded by ROBINSON (1926), in the *11th and 12th Reports of the Director of Veterinary Education and Research*, Union of South Africa, in regard to the differences in antigenic affinity, and hence presumably in chemical composition, displayed by the three great groups of pathogenic mammalian trypanosomes (the paper has come to the author's notice since the manuscript of this Memoir was sent to the Press). Using a *T. equiperdum* antigen, ROBINSON found that the serum of animals infected with *T. brucei* reacted with it in the complement fixation test; the serum of animals infected with *T. congolense* gave only partial reactions in the test, and these but rarely, whilst no reactions were obtained with sera from cases of *T. vivax* infection.

[2] According to KLEINE (1924) the nucleus of " Bayer 205 " is trypanblue and the product is built round trypanblue in much the same way as in Ehrlich's elaboration of salvarsan from atoxyl. FOURNEAU, TRÉFOUEL, and VALLÉE (1924) have discussed at length the question of the chemical constitution of " Bayer 205 " and have arrived at the provisional conclusion that the drug is a urate of meta-aminobenzoyl-para-methyl-meta-amino-benzoyl-I-amino-naphthalene-trisulphate of sodium-4-6-8. They have prepared a substance which they designate as " 309 " and which they believe is identical with " Bayer 205." VAN SACEGHEM (1925) tested " 309 " on cattle infected with *T. cazalboui* var. *vivax* and *T. congolense-pecorum*. The drug was used in a 25 per cent. solution. Experiments on four animals showed that the drug cleared the blood of trypanosomes for about one week only. One animal died six days after receiving a dose of 4 grams per kilo.

as not being of the same therapeutic value (from a qualitative or quantitative point of view or from both).

It may be mentioned that at Muktesar a difference in toxic effect was believed to have been observed between two samples of drug received from the Bayer firm, for whilst with the first consignment toxic symptoms were not marked until dosages of 10 grams per 1,000 lb. body weight were administered intravenously to a series of horses, with the second consignment (used in nearly all the experiments carried out subsequently to 22nd September 1925) symptoms were often very distinct after the administration of the drug at the rate of 5 grams only.*

The dosage of "Bayer 205."

In the rules laid down by MAYER (1922) for the use of "Bayer 205" in the treatment of human trypanosomiasis, he recommends the employment of small doses —0·5—1, up to 3 grams administered within a week, followed by at least 14 days' interval. For the treatment of affections of a mild character and for purposes of prophylaxis, the dosage recommended by him is 1-2 grams repeated every four weeks. Treatment by means of small doses would, however, appear to be undesirable in view of the possibility of the development of "drug-fast" strains (see chart of Horse 59, although, obviously, this possibility did not occur to MAYER by reason of his failure to obtain evidence of "drug-fastness" in the case of trypanosomiasis in small animals.

The observations of RUPPERT (1923) relative to the variability of the chemotherapeutic quotient of "Bayer 205" for different species of animals are of especial significance in their bearing upon the manner in which the drug should be employed in actual practice. RUPPERT emphasizes the fallacy of making deductions in regard to dosage for large animals from the results obtained from experiments conducted on small animals. He points out that whilst the therapeutic index of "Bayer 205" for mice is 1 : 400, that for rabbits (infected with *T. equiperdum*) is 1 : 10, and that for horses (infected with mal de caderas) is only 1 : 2. The lethal dose was found to be about 0·5 to 0·6 gram per kilo for rabbits and 1 gram per 50 kilos for horses (*i.e.*, 0·02 gram per kilo), so that the drug is 25 times as toxic for horses as it is for rabbits. The difficulty of ascertaining the dosage from the results of experiments carried out on small animals is particularly exemplified in the treatment of chronic affections. As RUPPERT points out, although in the case of mice the therapeutic index of atoxyl, salvarsan, and silversalvarsan is 1 : 2 to 1 : 3, 1 : 10, and 1 : 22, respectively, nevertheless atoxyl is more efficacious than the other two drugs in the treatment of men and larger animals. The reason for this, according to him, is that the drug is absorbed and excreted differently in different animals, so that the dosage must be determined separately for each species of animal.

* These results were communicated to the Bayer firm and they wrote in reply that they were unable to account for the difference, which was entirely unanticipated. In a communication dated 16th August 1925, addressed to the writer, they observe: "It is quite a new fact to us that after having administered 10·0g Naganol per 450 kilo body weight in a horse, pododermatitis appeared. Anyhow, we certainly agree with you that in horses the dosage should not overgo more than 5·0 grams."

Compared with horses, cattle would appear to be capable of tolerating quite large doses of " Bayer 205 ", for, whilst according to RUPPERT the lethal dose for horses in only 1 gram per 50 kilo body weight, VAN SACEGHEM (1924) observed that the fatal toxic dose for cattle was 7·5 grams for the same body weight.

A critical study of the question of dosage for small animals was made by LANGE and KERSTEN (1924), who refer to certain discrepancies in the observations made by previous workers in regard to the toxic dose of " Bayer 205 " for mice. HAENDEL and JOETTEN found the toxic dose to be 18 to 20 mgm. (occasionally 30 mgm.), while MAYER and ZEISS, and MIESSNER and BERGER found it to be 10 mgm. and 10 to 15 mgm. respectively. LANGE and KERSTEN's observations were in accord with those of HAENDEL and JOETTEN, although the toxicity was found to be slightly higher with a 41 months old solution of the drug.

The therapeutic dosage of " Bayer 205," as employed in the treatment of various forms of trypanosome infection in horses, appears to have been subject to considerable variation.

The dosage employed by SCHMIDT and DE OLIVEIRA (1924) was 2-3 grams for the treatment of horses and mules infected with mal de caderas, a total of 7 to 9 grams being found sufficient to effect a cure.

MIGONE and OSUNA (1922) record the results of a series of experiments on the curative effect of " Bayer 205 " on four horses infected with mal de caderas. Two of the horses weighed 250-300 kilos and the other two, 200 and 150 kilos, respectively. The larger animals were injected intravenously with 7, 4, and 3 grams at intervals of 15 and 8 days ; the smaller animals received 2 grams and subsequently 3 and 4 grams at intervals of 8 days. As the result of the experiments, the authors recommend, for curative purposes, doses of 2, 3 and 4 grams of the drug at intervals of 8 days, since toxic symptoms were produced in the case of the two animals which were treated with larger doses.

PATAKI (1923) obtained what would appear to be encouraging results in the treatment of dourine by means of " Bayer 205 " administered in doses of only 0·01 gram per kilo.

In the treatment of *Trypanosoma venezuelense* infection, which levies a heavy toll on horses in Venezuela, TEJERA (1924) found that, whilst a single injection of 4 grams was inadequate, a second dose of 3 grams administered at an interval of 10 days was effectual.

BALOZET, LAVIER, and VELU (1923), record a striking instance of success obtained in the treatment of a horse severely affected with dourine, by means of " Bayer 205 " injected intravenously during a period of 4 days, in three doses totalling 7 grams.

BAERMANN (1922), who would appear to be the earliest worker to test the efficacy of " Bayer 205 " upon horses affected with surra in the Dutch Indies, used the drug intravenously either in a single dose of 5 to 10 grams or in three to five doses, totalling 8 to 25 grams, administered at short intervals.

In their experiments upon the treatment of equine surra by means of "Bayer 205," RODENWALDT and DOUWES (1922) administered the drug intravenously either in single doses, genera ly of 5 grams, or in small doses of 0·25 gram to 1·7 grams, repeated usually on alternate days, until a total of about 10 to 15 grams had been reached.

BUBBERMAN, DOUWES, and VAN BERGEN (1925), in an extensive series of experiments upon the treatment of equine surra, used "Bayer 205" either in fractional doses of from 0·5 to 2 grams or in large doses of 3 grams, in combination with tartar emetic or atoxyl or both.

The dosage employed by BAKKER (1925) in the treatment of the same disease ranged from 1 to 4 grams until a total of 4 to 9·2 grams had been reached. The drug was used in combination with tartar emetic and atoxyl.

In view of the results already available relative to the safe therapeutic dose of "Bayer 205" for horses, it was deemed unnecessary to undertake extensive experiments directed particularly with the object of ascertaining the minimum lethal dose of "Bayer 205" for these animals. A careful analysis of the results recorded by previous workers coupled with those obtained in the course of preliminary experiments (see protocols of three horses, Nos. 21B, 26 and 28, injected intravenously with "Bayer 205," at the rate of 5, 7·5, and 10 grams, respectively for 1,000 lb. body weight) and the subsequent experience gained in treatment of infected subjects indicated that the safe therapeutic dose for intravenous administration was 5 grams (50 c.c. of a 10 per cent. aqueous solution) per 1,000 lb. body weight. The dose was found to be generally well borne, although in several instances its administration was followed by the onset of laminitis of varying degrees of intensity and duration, which, however, eventually disappeared. It was also found that repetition of this dosage, even after an interval of one month in one series of tests, was followed by the appearance of more severe symptoms than were observed in the same animals following upon the initial injection. This observation is of interest in view of what has to be said later regarding the retention of the drug in the system of horses after injection.

Toxic symptoms after "Bayer 205."

The occurrence of toxic symptoms following upon the administration of "Bayer 205" has been recorded by a large number of workers. Instances of the occurrence of more or less pronounced albuminuria in human beings have been cited by numerous observers, whilst in animals untoward effects have generally manifested themselves in the form of marked locomotor disturbances, urticaria, and œdematous swellings of a transitory character.

The toxic symptoms observed by MIGONE and OSUNA (1922) in a horse affected with mal de caderas and treated with "Bayer 205" were swelling of the hind quarters, pharynx and testicles and the appearance, on the fourth day, of eczema around the anus, on the nasal mucous membrane, and parts of the genitalia, these symptoms disappearing, however, in the course of 8 to 10 days.

PATAKI (1923) observed that the administration of "Bayer 205" to horses affected with dourine caused swellings and even necrosis of the skin and in several cases he obtained evidence of inflammation of the coronets.

BAERMANN (1922) noted in the course of his experiments on the treatment of equine surra that the administration of "Bayer 205" in too large doses caused podo-dermatitis and albuminuria accompanied with wasting and anæmia.

RODENWALDT (1923), who would seem to regard the drug with positive disfavour in regard to its efficacy in the treatment of equine surra, gives a graphic description of the toxic symptoms resulting from its administration and observes that the injection of "Bayer 205" in very large doses frequently causes death of the animal in 24 hours with generalized urticaria. The mucous membrane of the mouth, lips and tongue presents some superficial incrustations, and when these disappear, a number of more or less deep erosions are left behind. These lesions impede mastication, the mouth emits a fetid odour and the animal becomes emaciated. Ulcerations of a similar kind also appear on the mucous membrane of the rectum, where they may extend to the deeper tissues and cause abscesses which cicatrize very slowly. He also frequently observed the occurrence of a dermatitis on the limbs, shedding of the hairs, and a hypersensitiveness of the skin. The animal thus intoxicated appears uneasy in the standing position, the flanks are tucked up, and the gait is laborious. The coronets are swollen and hot. The hoofs are painful to the touch. In the case of severe intoxication, emaciation is rapid and death ensues within a short period of time. If the animal recovers, its recovery is very slow. The intoxication always leads to the formation of circular rings on the hoofs similar to those observed as a sequel to severe laminitis.

RODENWALDT and DOUWES (1922) give details of treatment of 21 horses from which it would appear that no matter in what quantities the drug was employed, the animals showed definite symptoms of intoxication, which generally progressed to a fatal issue, or the animals had to be destroyed *in extremis*. Moreover, these symptoms were not restricted to any special breed of animal, inasmuch as they were observable both in native ponies (from Java) and in large Australian horses.

Whilst the observations of RODENWALDT and DOUWES are entitled to careful consideration on account of the care with which they have been recorded, they would appear, on the other hand, to be remarkable in view of the fact that the occurrence of such untoward effects following upon the administration of the drug has not been recorded by previous workers, and is certainly contrary to our experience with it at Muktesar. The largest single dose of "Bayer 205" administered by RODENWALDT and DOUWES did not exceed 5 grams, whilst in the course of the experiments recorded in this paper, the drug was administered in one instance (Horse 28) at the rate of 10 grams per 1,000 lb. body weight and in another instance (Horse 26) at the rate of 7·5 grams per 1,000 lb. body weight, and yet no untoward results appeared beyond the occurrence of urticarial eruptions, œdematous swellings, slight albuminuria and moderately distinct laminitis, all of which symptoms

passed off completely within a few days; in the case of the horse administered the larger dose, the albuminuria disappeared within nine days and the symptoms of laminitis almost entirely in 15 days. It has been stated, however, that repetition of the dosage prior to the lapse of a somewhat prolonged interval, over a month, is fraught with greater danger of intoxication, apparently due to the long retention of the drug in the system after injection (see protocol of Mare 57, fatal intoxication in horse in low condition; also Horse 70).

Intrathecal injection of "Bayer 205."

The results of our earliest experiments upon the treatment of horses at a stage when surra infection was established at a fairly advanced stage in their systems convinced us that, in exploiting adequately the possibilities of experimental therapy, account must be taken of the serious factor of cerebro-spinal involvement and the relative futility of combating this phase of the disease by intravenous medication. The records of three horses (Nos. 19, 3 and 2) inoculated at the same stage of infection, intravenously, with "Bayer 205" at the rates of 1, 2·5, and 5 c.c. per 1,000 lb. body weight respectively, demonstrated that, although prolonged clearance of the blood circulation could be attained with a suitably large dose, the animals succumbed, nevertheless, to acute infection of the cerebro-spinal system. Investigations were, therefore, planned with a view to ascertaining the possibilities of attacking the parasites direct in what might be regarded otherwise as the safe retreat of the cerebro-spinal canal, by intrathecal injection in addition to the intravenous administration of the drug.

In spite of the claims that have been made for various drugs, notably tryparsamide, in regard to their property of so-called "penetrability," cerebro-spinal involvement in trypanosomiasis constitutes a phase with which it has been most difficult, or almost impossible, to deal. This phase of infection is very familiar to workers with human sleeping sickness, and it cannot fail to escape notice that in dourine it is likewise the aspect of the affection that ought to demand close therapeutic study. Intrathecal injection as a mode of drug administration would appear to have found but little application in the treatment of trypanosome infections, particularly in the domesticated animals, although a section of American syphilologists treat all cases of human syphilis at the present time by intraspinal as well as intravenous injection of salvarsan or one of its modifications with a view to preventing the possibility of cerebro-spinal complications, in the form of locomotor ataxy or general paralysis of the insane, which may develop some years after an apparent cure of the primary or secondary lesions after intravenous injection alone. Tryparsamide seems to have found much favour for this purpose.

Van den Branden and van Hoof (1924), who have published what would appear to be valuable observations upon a large number of cases of sleeping sickness treated by means of "Bayer 205," state that in the case of three patients treated by combined intravenous and intrathecal injection the results obtained were very

unsatisfactory, and the authors refer to the grave risks that attend the intrathecal administration of such a small dose as 0·05 gram, whilst the administration of 0·3 gram may, according to these observers, lead to fatal results.

TANON and JAMOT (1924) record cases of sleeping sickness in which the intrathecal injection of "Bayer 205" was followed by serious consequences, and the authors abandoned this form of treatment after two consecutive failures, the patients having succumbed shortly after the injection. The first patient, a female aged 20 years, in the third stage of the disease, who had been suffering for two years, received a large dose of 0·5 gram and death occurred within 7 hours with cardiac troubles terminating in abrupt syncope. The second patient was a vigorous youth of 25 years at the commencement of the second stage of the disease. He received a dose of 0·25 gram and death followed within the brief space of 4 hours with the same symptoms as were observed in the first case.

The observations recorded by the above authors indicate, however, on analysis, that the doses employed by them were too large for the purpose of intraspinal medication and that the grave consequences to their patients might have been averted if in estimating the dosage suitable for employment they had been guided by a consideration of the weight of the cerebro-spinal tissues relative to the weight of the rest of the body and administered intrathecally a quantity of the drug bearing this ratio to that capable of safe employment in intravenous medication. Simple arithmetic calculation from the figures given in text books of anatomy and some observations in the *post-mortem* room at Muktesar showed that this ratio in the case of the horse amounted to approximately 1 : 500. Moreover, in our experiments the dosage of "Bayer 205" that could be safely injected subdurally (or, more correctly into the subarachnoid space) was carefully estimated by titration on horses, as shown in Table II.

It will be seen from this table that Foal 56 died (or, rather, was put to death *in extremis*) one and a half hours after receiving a dose of 0·5 gram per 1,000 lb. body weight whilst the other two animals (Foal 49 and Foal 72) both of which received the drug at the rate of 0·2 gram per 1,000 lb. body weight, in different dilutions, survived. Foal 49 exhibited no toxic symptoms except for a small degree of pruritis, but Foal 72 staggered shortly after receiving the injection, although it eventually recovered completely. The sequence of toxic manifestations exhibited by Foal 56 which succumbed to the injection was as follows :—

3·58 p.m. Received intrathecal injection. Got up and walked, but opened mouth as if to yawn from time to time. Increased respiration. Gait unsteady. Pawing ground. Fell down. Struggled on to feet. Seemed affected with visual disability (blinking eyes). Recovered somewhat. Pawing ground.

4·5 p.m. Fell down again, almost turning somersault. Lying down on side. Breathing heavily. Sitting. Got up. Apparently recovering. Struggling. Walked round very uneasily. Staggering. Seemed to be looking more easy and recovering control.

4·15 p.m. Fell down, became entangled with halter rope, and unable to get up. Lying down on its breast with hind legs apart. Tried to get up but failed. Seemed to be losing power in hind quarters. Lying down on side with legs outstretched. Breathing heavily. Breathing "jerky" in character. Eyes closed. Struggled and tried to get up but failed. Seemed to lack power in fore quarters. Lying on breast with fore-legs extended together in front. Opened mouth. Breathing heavily. Noise in throat as if suffering from partial paralysis of glottis. Struggling violently. Neighing as if affected with mania.

4·35 p.m. Lay down quietly again. Struggling to get up and rolling from side to side. Lying with head below its body. Struggling violently and causing damage to its mouth by hitting jaw against ground and struggling to get up but falling on side. Struggling again violently. Lying down and making violent efforts to get on feet causing much injury to jaw.

4·46 p.m. Struggling violently with head towards chest.

4·49 p.m. Defecated.

4·51 p.m. Still struggling from time to time violently.

5·7 p.m. Neighing and biting paving stones as if affected with mania.

5·24 p.m. Chloroformed to death.

The results indicated that a dose of 0·5 gram per 1,000 lb. body weight was definitely toxic for horses and that a dose of 0·2 gram per 1,000 lb. body weight constituted what might be regarded as the "subtoxic" dose. A point that is probably not unworthy of notice in connection with intrathecal medication is the dilution of the drug administered, for, contrary to what occurs with intravenous injection of a drug, rapid dilution does not take place, it would seem, after introduction of the drug solution into the cerebro-spinal fluid, and hence if the drug is present in the solution employed in high concentration it may be liable to exercise a toxic action immediately on the sensitive tissues adjacent to the seat of puncture.

The safe dose for administration by the intrathecal route was then fixed at 0·02 gram per 1,000 lb. body weight, or 20 c. c. of a 0·1 per cent. solution. This quantity assured the subjection of the cerebro-spinal tissues of the horse to as strong a concentration of the drug as that to which the other tissues of the body were subjected when the maximum safe intravenous medication was applied, and represented, as disclosed by experiment, an amount that was not susceptible of giving rise to symptoms of intoxication. The above dilution for intrathecal injection was conveniently made up by placing in a sterile 100 c.c. measure, one c.c. of the 10 per cent. solution used for intravenous injection and adding to it 99 c.c. of sterile water or "normal" salt solution, the mixture being well shaken afterwards.[1] The records of experiments further showed that this dosage could be safely repeated at fortnightly

[1] It is of interest to recall in this connection the experiments of CORREA MENDES (1907), who injected intrathecally 10 c. c. of a 1 per cent. solution of atoxyl in the treatment of human sleeping sickness. KOPKE (1907) and THIROUX and D'ANFREVILLE (1907) also used similar injections, usually in advanced cases. (Cited in *Bulletin of Sleeping Sickness Bureau*, Vol. 1, p. 7.)

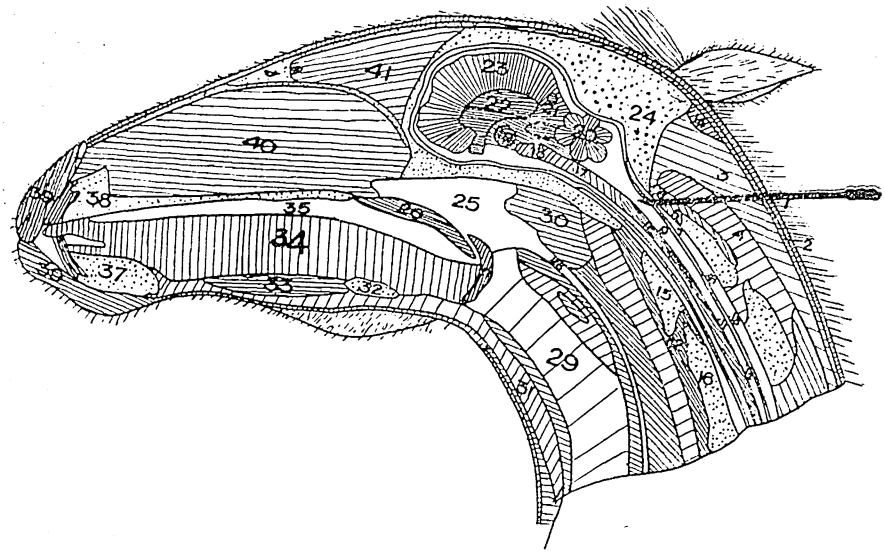


Fig. 1.

Diagrammatic representation of a sagittal section of a horse's head to illustrate the relationship of the parts adjacent to the seat of intrathecal puncture.

1. Skin.
2. Cervical panniculus.
3. Ligamentum nuchae.
4. Rectus capitis sup. major.
5. Rectus capitis sup. minor.
6. Dorsal atlanto-occipital membrane.
7. Epidural space.
8. Subdural space.
9. Subarachnoid space.
10. Spinal cord.
11. Pia mater.
12. Arachnoid membrane.
13. Dura mater.
14. Cervico-auricularis muscle.
15. Atlas.
16. Axis.
17. Medulla.
18. Pons.
19. Thalamus.
20. Cerebellum.
21. Pineal body.
22. Corpus callosum.
23. Cerebral hemisphere.
24. Occipital bone.
25. Pharynx.
26. Soft palate.
27. Epiglottis.
28. Œsophagus.
29. Trachea.
30. Septum between guttural pouches.
31. Omo and sterno-hyoideous muscles.
32. Hyoid bone.
33. Genio-hyoideous.
34. Tongue.
35. Oral cavity.
36. Hard palate.
37. Body of mandible.
38. Body of premaxilla.
39. Lip.
40. Septum nasi.
41. Septum between frontal sinuses.
42. Rectus capitis inferioris.

Fig. 2. Intrathecal puncture and withdrawal of cerebro-spinal fluid.

Fig. 3. Intrathecal injection of " Bayer 205."

intervals (see protocols of Horse 63 and Ponies used in experiment upon relative value of combined intravenous-intrathecal treatment, p. 25)

The method used for the operation of intrathecal injection in equines was as follows :—

The horse is cast and securely tied down, with its head towards its chest; with a right-handed operator it is more convenient to have the horse cast on its right side. An area of hair and mane is clipped just over the poll, and painted with tincture of iodine. A sterilized injection needle, about 6 inches in length and $\frac{1}{16}$th to $\frac{1}{8}$th inch in internal calibre, with a well-made, firm, sharp point, is then thrust firmly and gradually through the mesial line of the poll, slightly deviating from the perpendicular downwards and forwards, at a distance of three to five inches (varying with the size of the animal) behind the occipital crest. The point of the needle is thus directed towards the occipito-atlantal space, and when it is estimated that the membrane closing the space is nearly reached, at a distance of about one and a half inches below the level of the skin the needle is cautiously thrust a short distance at a time, until ultimately, on awaiting a little after a propulsion clear cerebro-spinal fluid streams away from the outer orifice of the needle. Care is taken to withhold further propulsion or displacement of the needle, so as not to risk penetration of the medulla. In this situation, the point of the needle will have traversed through the dura mater and arachnoid membrane into the subarachnoid space (see Fig. 1 illustrating diagrammatically the relationship of the tissues at the seat of operation), and the success of the operation would seem to depend largely upon the capacity of the needle point to traverse cleanly and immediately, without pressing it forward in the thrust or lacerating it, the delicate arachnoid membrane; hence, it is important to use highly polished, sharply ground, unworn needles for the operation. Sometimes it happens that the needle point encounters some firm resistance in the course of its trajectory, usually in the form of the inferior extremity of the occiput; in this event, the needle is immediately withdrawn a short distance and then redirected along a somewhat more posteriorly direction. Some accidents occurred in performing the puncture before the above details of procedure were appreciated, but with experience the risk became a very small one, and it ought to be capable of performance with safety by any careful operator after a little practice. Cerebro-spinal fluid may thus be withdrawn in abundance for examination, and afterwards intrathecal injection of fluids performed, by slipping on the butt of the needle a short length of india-rubber tubing the other end of which is tightly secured to the nozzle of the injection syringe; this has been the method hitherto adopted, but it might answer almost as well if the needle were made so that it could be connected direct with the syringe, although the rubber connection provides a factor of safety in the event of the horse struggling. It can be readily ascertained when the fluid enters the subarachnoid space successfully, by its smooth passage with little pressure applied to the piston rod, and a tendency for the regurgitation of cerebro-spinal fluid into the syringe barrel when the pressure on the piston is relaxed if the syringe is fitted with a piston that glides lightly within the barrel. (See photographs illustrating operation, Figs. 2 and 3.

Initial peripheral sterilization.

Before undertaking any extensive series of experiments relative to the curative value of " Bayer 205 " in the treatment of equine trypanosomiasis, it was considered desirable to ascertain the approximate rapidity of the sterilizing effect of a single dose of the drug, as determined by repeated microscopic examination of blood films (fresh preparations) and also by subinoculation of blood into guinea-pigs and rabbits.

MAYER and ZEISS (1920) found that " Bayer 205 " cleared the blood of trypanosomes in 12 hours in the case of small animals experimentally infected with *T. brucei*, *T. gambiense*, *T. equiperdum*, and *T. equinum*, although *T. cruzi* proved somewhat refractory to the treatment.

MIGONE and OSUNA (1922) record an instance of mal de caderas in which the trypanosomes disappeared completely within 36 hours after the injection of the drug.

HERZOG and LAVIER (1923) record the history of a case of debab in which a dose of 4 grams of " Bayer 205 " was injected intravenously and on the following day trypanosomes were not discoverable in the blood and the animal was in excellent condition six months later. The author remarks that the fact that sterilization can be effected by a single injection is of practical importance in a country where animals cannot be kept under observation for prolonged periods.

In the course of the present series of experiments, it was observed that the minimum period required for clearing the blood of trypanosomes by means of a dose of 5 grams of " Bayer 205 " per 1,000 lb. body weight was somewhat under 12 hours (Horse 64), whilst with a dose of 1 gram the minimum period required was somewhat over 24 hours (Horse 53). The relative slowness and remarkable steadiness of the trypanocidal action must be regarded as constituting two of the outstanding virtues possessed by the drug which render possible its administration in full therapeutic dosage in more or less advanced cases with intense parasitic blood invasion where the administration of drugs like tartar emetic is contra-indicated by reason of their drastic trypanocidal action resulting in the occlusion of capillaries with dead trypanosomes or in the liberation of toxic decomposition products (BUBBERMAN and collaborators, 1925).

Reference to Table III will show that in a number of cases a periodical examination of blood films was undertaken with a view to determining the degree of rapidity with which sterilization was effected, and in one case (Horse 64) the results of examination of blood films were confirmed by subinoculation of the blood into guinea-pigs (Table XVII). What may be regarded as the quantitative sterilizing effect of the drug is exhibited in the results shown against Horse 53 and Horse 64, for, as has already been stated, whilst in the first case treated with 1 gram per 1,000 lb. body weight the trypanosomes persisted in the circulation even 24 hours after treatment, no parasite was discoverable 12 hours after treatment in the case of Horse 64 which had received an intravenous injection of the drug at the rate of 5 grams per 1,000 lb. body weight.

It is noteworthy that whether the animals had been previously prophylactically treated or not, complete sterilization of the blood was generally effected within a period not exceeding 24 hours following upon a single administration of the drug at the rate of 5 grams, although, under certain conditions, the subsequent course of the infection furnished evidence of what would appear to be a certain degree of " drug fastness " having been acquired by the organisms. This point will be discussed later in this paper.

It should be pointed out, however, that the above generalization, namely, that the administration of the drug in the full therapeutic dose brought about sterilization of the blood in the course of 24 hours, does not imply that an examination one or more hours previous to the negative finding was positive, for a glance at Table III will show that in the majority of cases the blood examination was not made earlier than 24 hours after the injection of the drug, and, as has been already stated, in the only instance (Horse 64) in which such examination was made, the blood stream was found to have been cleared of the trypanosomes in the course of only 12 hours following upon the administration of the " Bayer 205," but was positive at the examination made at the 6th hour after the injection of the drug.

KLIGLER and WEITZMAN (1925) observed that in the case of *T. evansi*, exposure of the parasites *in vitro* to varying dilutions of " Bayer 205 " completely destroyed or considerably reduced their virulence, as proved by the results of subsequent inoculations of the organisms into guinea-pigs, although they still showed active movement. In the course of the present investigations, the results of the only experiment (Horse 64) designed to furnish information on this point showed that the trypanosomes remained infective to guinea-pigs during the whole of the period between treatment and their final disappearance from the blood stream. It is, however, proposed to carry out a further series of experiments with a view to elucidating this point.

Duration of peripheral sterilization after the administration of single doses of " Bayer 205."

There would appear to be few instances on record of permanent recovery having been effected as a result of the intravenous injection of a single dose of " Bayer 205," and some form of repeated dose therapy has been recommended by most workers for the prevention of relapses. As with all other trypanocidal agents, it would seem to be generally held that the permanence of the therapeutic effect obtained by the administration of " Bayer 205 " cannot be maintained for an indefinite period and relapses eventually occur sooner or later. With a view to forestalling the occurrence of relapses in equine surra, BAERMANN (*l.c.*) recommends that after an initial dose of 2 to 2·5 grams per 50 kilo body weight, two or three 1 to 1·5 gram doses of the drug should be administered at intervals of 25 to 35 days, although he records instances in which infected horses treated with single injections of " Bayer 205 " did not relapse during observation periods which varied from 2 to 11 months.

In the experiments described by RODENWALDT (*l. c.*) the infected horses, if they did not die of intoxication, invariably relapsed after receiving the drug in doses varying from about 0·25 to 5 grams.

It may be remarked that the system of repeated dose therapy directed with the object of merely maintaining the peripheral blood in a state of sterilization will continue to remain unredeemed from empiricism until further light has been thrown on the genesis of relapses themselves. YORKE (1921) has questioned the validity of MARSHALL'S assumption that post-treatment relapses are due to re-infection of the blood by parasites which "quite early in the disease" gain an impregnable position in the central nervous system where they are protected from the action of the drug. With the caution characteristic of his critical reviews, YORKE remarks: "That it is an adequate explanation why, to quote MARSHALL'S words, 'attempts to cure patients infected with trypanosomes have, in the vast majority of cases, proved unsuccessful,' cannot, however, be accepted without very careful and searching enquiry." Later in the same paper, YORKE summarizes the situation as follows: "There appears no reason to doubt that the blood stream may be re-infected from the cerebro-spinal fluid, if the latter is already invaded, and that this may, in part at least, explain the relapses which occur after treatment in advanced cases; such a mechanism cannot, however, explain the post-treatment reappearance of trypanosomes in the blood of earlier cases where there is no reason for believing that the nervous system is involved; in these cases the blood stream, provided it is really sterilized by the drug, must be re-infected from circulation back-washes, or from tissue spaces, where the parasites have been able to exist protected from the medicant circulating in the blood."

Whilst the views expressed by a critic of YORKE'S eminence must be regarded as entitled to careful consideration, nevertheless in any scheme of curative treatment based upon a system of single or repeated dose therapy the immediate course indicated would appear to be to attempt a sterilization of the cerebro-spinal fluid concurrently with that of the circulatory system, with a view to preventing the invasion of the meninges, which eventuality has been generally regarded as the terminal and almost irremediable phase of all forms of trypanosome infection. Incidentally, a series of investigations conducted on these lines would also be calculated to furnish valuable evidence concerning the origin of relapse strains.

It is difficult to appreciate sufficiently well the effects of treatment by the succinct exposition of results concerning a number of cases in tabular form; such appreciation is best obtainable by observing the daily progress of the experimental animals under one's charge for the prolonged periods of time demanded in this class of investigation, as is recorded in the charts and protocols attached to this paper. Table IV, however, attempts to summarize the records of 34 horses treated intravenously with single doses of "Bayer 205" of from 1 to 5 grams per 1,000 lb. body weight; 21 of these animals received, in addition, an intrathecal

injection of the drug at the rate of 0·02 gram per 1,000 lb. body weight. The results may be briefly indicated as follows :—

(*a*) *13 treated with intravenous injection alone.* Of these 4 relapsed in post-treatment observation periods ranging from 8 to 47 days. Of the relapsed cases, three animals had, however, received a dose of only 1 gram per 1,000 lb.

(*b*) *21 treated with combined intravenous and intrathecal injection.* Of these only three relapsed during post-treatment observation periods of 21, 21, and 45 days (in one of these cases tryparsamide, instead of "Bayer 205", was used for intrathecal injection). As will be seen from Table V, several of the non-relapsed cases were later transferred to the repeated dose schedule. It should be mentioned that two of the relapsed cases (Mare 57 and Horse 28) had been previously treated prophylactically with "Bayer 205," so that in the interpretation of the results due regard has to be paid to the possibility that the organisms had acquired a certain degree of resistance to the drug.

The results obtained, for example, in the case of Horse 3 strikingly illustrate the fallacy of declaring an animal trypanosome-free from the indications furnished by mere blood examinations. On reference to the protocol of this animal, it will be observed that, although at the time of death the blood examination was quite negative for trypanosomes, a cover glass preparation of centrifuged cerebro-spinal fluid was found to be swarming with trypanosomes, so that the animal doubtless succumbed to the effects of invasion of the cerebro-spinal axis.

Reference to the records of the experiments show, however, that a single intervention with a sufficiently large dose of the drug applied very early in the course of the development of infection, even by intravenous administration alone and after introduction of the infective material directly intrathecally, is capable of bringing about a definite sterilization. (See protocols of Horse 67, and donkey experiments.)

Treatment with repeated doses of "Bayer 205."

On the other hand, our earliest trials in therapy demonstrated that intravenous medication with single doses of "Bayer 205" were not destined to meet with lasting success in cases in surra that had progressed to the stage when their clinical features would call most ordinarily for the application of special treatment if they had been natural cases occurring in the field. In the preliminary therapeutic experiment upon three well established cases of infection to which reference has already been made, intravenous medication at the rate of 1 gram per 1,000 lb. body weight was followed by death in 23 days, with a fairly well marked trypanosome septicæmia prior to death. After administration at the rate of 2·5 grams, however, no blood invasion was detectable subsequently at any stage, but nevertheless the horse died in 30 days, with symptoms of intense cerebro-spinal disease and a rich invasion of the cerebro-spinal fluid with trypanosomes. In the case

of the third horse administered the drug intravenously at the rate of 5 grams, the period of survival extended to 49 days, when it succumbed after displaying marked paraplegia and paralytic symptoms, with a slight blood invasion just before death. As further experience showed, drug intervention *in extremis* was likely again to prove quite fruitless (see protocol of Horse 45). Moreover, the information forthcoming from the experiments upon the prophylactic action of the drug, which is discussed in a later section, indicated that after intravenous administration in full therapeutic dose it was present in trypanocidal concentration in the blood for about three weeks afterwards, and in a dilution that had an inhibitory, although not a destructive, effect for probably two months. Hence it would appear to be a sound plan to repeat the administration of the therapeutic dose after a month's interval, and this view received support from the results of actual experiments in this direction (see Horses, 68, 69, 70, treated on 23rd September 1925 and 23rd October 1925).

Repeated intravenous application of small doses of " Bayer 205 " would appear, however, to be distinctly contra-indicated except, possibly, in cases where the subjects have become so much depressed in physical condition that the administration of the full therapeutic dose initially would be fraught with some risk. As is illustrated by the protocol of Horse 59, the injection of " Bayer 205 " intravenously at the rate of 1 gram per 1,000 lb. body weight during the course of infection leads only to a temporary disappearance of the trypanosomes from the blood stream, and a repetition of the dosage with each relapse arising subsequently is followed by an appreciable diminution in the effect of the drug with each administration. Hence the exposure of trypanosomes to subtoxic concentrations of the drug in the blood seems to be an eventuality to be avoided, and EHRLICH'S conception of a *therapia sterilisans magna* would find justification from the results of experience in the application of treatment with this drug.

Table V summarizes the protocols of 19 horses which were treated with more than one dose of " Bayer 205." It will be seen that all the five animals that died of trypanosomiasis had been treated by intravenous injection only (the intrathecal treatment received by Mare 2 and Horse 59 may be left out of consideration for practical purposes) and a reference to Table IV will show that of these five animals, as many as three represented relapsed cases. Three of the animals died in spite of having previously received the drug both by the intravenous and intrathecal route, although none of these at the time of death showed trypanosomes in the blood or in the cerebro-spinal fluid. On autopsy, however, two of the animals (Nos. 57 and 85) showed evidence of having died of intercurrent disease (schistosomiasis and pleuro-pneumonia, respectively), whilst the cause of the death of the third was undetermined.

Combined intravenous-intrathecal administration of " Bayer 205."

It was realized that an appraisal of the relative value of the combined injection and the intravenous injection alone must be based upon the interpretation of the

experimental results obtained under strictly comparable conditions, and a number of attempts were made to obtain appropriately controlled results in this manner. Reference to the protocols appended to the paper will furnish the records of five infected horses (injected on 23rd-24th September 1925 and 23rd October 1925 ; Horses 69, 21A, 68, 70 and 64) in which tests were carried out with this end in view ; two were given the combined treatment using " Bayer 205 " for intravenous and intrathecal injection, two were injected intravenously with " Bayer 205 " and intrathecally with tryparsamide, and one horse was given " Bayer 205 " intravenously alone ; in all cases, the treatment was repeated after a month's interval. The results are inconclusive as the horse treated intravenously alone (the one that was in the earliest stage of infection) has not given evidence of relapse.

A number of donkeys were also procured and infected by direct inoculation of virulent material intrathecally (see protocols). They were then treated by the administration of " Bayer 205 " intravenously-intrathecally (at the rate of 5 grams per 1,000 lb. body weight intravenously and 0·02 gram per 1,000 lb. intrathecally) at an early stage of the appearance of trypanosomes in the blood stream, while some donkeys were treated simultaneously in the same manner intravenously alone and in one instance (Donkey 30) the drug was administered, *in extremis*, intrathecally, without the concurrent intravenous injection. As will be seen, the donkeys treated intravenously alone as well as the other donkeys have not shown any sign of relapse, probably due to the intervention with treatment at too early a stage in the infection, while the control untreated donkeys succumbed early.

On the 27th November 1925, 12 ponies, specially procured for the purpose, were each inoculated intrathecally with 1 c. c. of blood containing a highly virulent strain of trypanosomes. Eight days after the infective inoculation, when trypanosomes were present in considerable numbers in the blood stream, nine of the ponies received " Bayer 205 " as follows :—

		Intravenous Dose per 1,000 lb.	Intrathecal Dose per 1,000 lb.
Group I	Pony 74, Pony 76	2·5 grams	..
	Pony 79, Pony 80	5 „	..
Group II	Pony 77, Pony 78, Pony 86	2·5 „	0·02 gram.
	Pony 84, Pony 85	5 „	0·02 gram.

The remaining three horses were used as controls ; of these, one (Pony 81) succumbed shortly after the infective inoculation owing to injuries, and the other two (Ponies 82 and 83) developed surra which rapidly progressed to a fatal issue (see

charts). The intrathecal treatment was repeated twice, on the 16th and 30th days, in the case of the ponies originally treated in this manner, while the intravenous inoculation was repeated once, on the 30th day, in the same manner as originally, in the case of all animals.

On 15th February 1926 (*i.e.*, 41 days after the last injection), Pony 76 showed trypanosomes in its blood and subsequently developed a mild type of infection. On 4th March 1926, it received the combined intravenous intrathecal treatment (at 5 grams and 0·02 gram per 1,000 lb. body weight) which caused a disappearance of trypanosomes from the blood, but it relapsed again on 27th April 1926. The intrathecal injection was repeated on 30th July 1926 and the intravenous injection on the following day, but the treatment was ineffectual and the animal succumbed on 12th August 1926. On 16th March 1926 (*i.e.*, 71 days after the last injection), Pony 74 showed trypanosomes in its blood ; it did not receive further treatment and died on 31st March 1926. The other animals* surviving in the experiment remained negative throughout the observation period which extended to 16th December 1926. It would seem, therefore, that the experiment had been planned upon suitable lines for the yielding of the desired information, and it is proposed to repeat it upon a larger scale at a future date. It will be noted that two of the five animals administered " Bayer 205 " intravenously at the rate of 2·5 grams per 1,000 lb., repeated after a month's interval, have relapsed, and that these two animals were given the drug intravenously alone, while the three animals that received intrathecal treatment in addition have not relapsed.

The results obtained do not, at any rate, controvert the idea that the combined intravenous-intrathecal medication is superior to intravenous medication alone, and the preliminary information available lends at least some support to the view that the combined treatment is capable of yielding more durable effects. Nevertheless, there would appear to be some evidence forthcoming also that repetition of the full therapeutic dose (5 grams per 1,000 lb. body weight) after an interval of a month, intravenously, without simultaneous intrathecal treatment, is capable of producing at any rate apparent recovery for a considerable period, even in equines that have undoubtedly harboured infection in the cerebro-spinal canal.

The prophylactic action of " Bayer 205."

Mayer and Zeiss (*l. c.*) in the course of their investigations upon the action of " Bayer 205 " on small animals experimentally infected with *T. brucei*, *T. gambiense* *T. equiperdum*, and *T. equinum* found that when employed prophylactically the drug prevented infection in mice for several months.

The prophylactic action of " Bayer 205 " against dourine was studied by Pfeiler (1922). Preliminary experiments showed that the drug conferred protection upon small animals which lasted for periods up to 200 days. For prophylaxis against

* Pony 85 died on 11th January 1926 from advanced pleuro-pneumonia.

this disease in horses the author recommends a total of 6 grams during the covering season, in doses of 3 grams administered at an interval of eight days. The prophylactic dose recommended by MIGONE (1922) against the same disease is 2 grams.

SCHMIDT and OLIVIERA (1924) observed that the protective action of " Bayer 205 " is the case of small animals experimentally infected with mal de caderas lasted for one month, whilst a mule and a mare, that had received 2 and 3 grams respectively, proved refractory to infection when injected with virulent blood after a fortnight and six weeks, respectively. DIOS (1925) used doses of 4 grams for prophylaxis against the same disease.

For prophylaxis against *T. venezuelense* infection in horses, TEJERA (1924) recommends a dose of 2 grams repeated every six months.

KLEINE and FISCHER (1922) found that monkeys treated with a subcutaneous injection of 0·15 gram of " Bayer 205 " resisted infection with *T. gambiense* for a period of at least one to two months. The prophylactic value of the drug for cattle would, however, appear to be very limited, for in the course of an address delivered before a meeting of the Royal Society of Tropical Medicine and Hygiene, KLEINE (1924) stated that even after large doses of " Bayer 205," *e.g.*, 10 grams for a bullock of about 5 cwt., repeatedly given, it was not possible to prevent infection by trypanosomes (the trypanosomes studied by KLEINE were *T. theileri*, *T. brucei*, *T. congolense*, and parasites of the *vivax* group). BERG (1925) also found the drug almost valueless, even when used in doses of 10 to 25 grams for the prophylactic treatment of cattle against *T. congolense* infection. It has already been remarked in discussing the therapeutic action of the drug that it may be of low efficacy against trypanosomiasis caused by organisms other than those pertaining to the so-called *brucei* group.

The results recorded by KLIGLER and WEITZMAN (1924) relative to the action of " Bayer 205 " upon guinea-pigs and rabbits experimentally infected with *T. evansi* would appear to indicate that, although the drug is capable of exercising prophylactic action, it does not prevent the disease from developing when administered during the period of incubation.

In regard to the prophylactic value of " Bayer 205 " against equine surra, BAERMANN (1923) found that protection from the disease lasting for about 30 to 42 days was conferred on three horses injected with 2 to 6 grams of the drug and subsequently inoculated, at varying intervals, with virulent blood.

BAKKER (1925) recommends a dose of 1 gram of " Bayer 205 " for the prophylactic treatment of horses in Padang Sidempoean where surra is widespread.

RODENWALDT and DOUWES (1923) state that as compared with its therapeutic value the prophylactic efficacy of " Bayer 205 " is greater and that treated animals may be protected from infection for many weeks.

In Table VI are summarized the protocols of 6 horses prophylactically treated with doses of " Bayer 205 " ranging from 1 to 10 grams, administered intravenously, per 1,000 lb. body weight. These experiments are among the earliest of the series

performed with the drug, for knowledge in regard to the duration of its retention in the system was considered essential in estimating the intervals that ought to be laid down for the repetition of the administration of the drug in the event of failure to produce complete sterilization by a single treatment. It will be seen that complete protection against artificial infection for a period extending to 22 days was obtained in an animal treated with a prophylactic dose amounting to 7·5 grams per 1,000 lb. body weight, and that inoculation of " Bayer 205 " simultaneously with the trypanosomes resisted infection even with the lowest dose of the drug administered. On the other hand, a dose as large as 10 grams per 1,000 lb. body weight failed to prevent the development of infection in an animal (Horse 28) that was injected with virulent blood about two months after the injection of the drug, although a very marked difference was noted between the course of the disease in this horse and that which occurred in a control horse inoculated at the same time with the same amount of the virulent blood employed ; the control horse succumbed within a few days to very acute infection, before the termination of the first febrile crisis. Whilst the period during which the drug can resist completely the development of a highly virulent infection would thus appear to be limited to a period less than 64 days, it is probable from the results obtained and the observations of other workers that the drug is capable of exercising a distinctly toxic action upon invading trypanosomes for at least a month after intravenous administration in full therapeutic dosage. It would seem to us that for horses continually exposed to the risk of natural infection in surra districts the prophylactic administration of " Bayer 205 " intravenously at the rate of 1 gram per 1,000 lb. body weight at intervals of a fortnight during the period of risk should be capable of warding off the disease.[1]

A point of considerable interest brought out in this Table when studied in conjunction with Table IV is that two of the animals (Nos. 57 and 28) which reacted to infective inoculation 64 days after the prophylactic treatment suffered relapses after a period of apparent recovery following upon a course of curative treatment with " Bayer 205." No relapse, however, occurred in the case of Horses 26 and 46 which were infected 77 and 74 days respectively after receiving the preventive inoculation. An analysis of these results points in the direction of the conclusion that the two relapsed cases represented in reality examples of " drug-fastness," as it would appear probable that after the prophylactic treatment residual quantities of the drug persisted in the circulation when the animals received their infective inoculation.

[1]While the page-proofs of this memoir have been under correction, the writer has had brought to his notice a paper entitled " The Prophylactic Action of ' Bayer 205 ' against Experimental Infection with a Trypanosome of the Formosan Water-Buffalo ", by Dr. Katsuya Kasai and Sasao Akazawa, published in the *Jl. Jap. Soc. Vet. Sci.*, Vol. VI, No. 1 (March 1927). The trypanosome isolated by them was " in all probability identical with *Trypanosoma evansi*, the causative agent of surra, according to its geographical distribution, as well as to its morphological characters and results of animal experiments." The authors found that in horses a subcutaneous injection of one gram of " Bayer 205 " per 100 kilo body weight failed to resist infection when they were inoculated with these trypanosomes one month after the prophylactic treatment, although their death, as compared with that of controls, was delayed. With double this dose of the drug, protection from infection was conferred for a period of 3½ months.

The observations are of obvious practical significance inasmuch as they are illustrative of the potential danger of unduly prolonging the interval between two successive protective inoculations, particularly in places where animals are constantly exposed to infection.

III. Treatment of Surra with Tartar Emetic.

From a perusal of the available literature, it would appear that, although tartar emetic has proved of value in the treatment of several forms of animal trypanosomiasis, in the majority of cases recorded it has been employed in combination with other drugs, and Blanchard and Laigret (1924) observe that it has yielded more encouraging results in the treatment of animal trypanosomiasis than in the treatment of human trypanosomiasis. In what follows a brief résumé is given of the results obtained by various workers by means of tartar emetic when used alone in the treatment of animal trypanosomiasis.

Hornby (1919), in summarizing the history of the employment of tartar emetic in the treatment of protozoan diseases, cites the following references :—Pecaud (1912) treated successfully eight cases of *T. dimorphon* (? *T. congolense*) infection of cattle by the administration of four or five doses of tartar emetic. De Greef found it useless by itself in the treatment of *T. cazalboui* (*vivax*) infection in horses, although cures were effected when it was used in conjunction with orpiment. On the other hand, Mouchet and Dubois (1913) state that *T. cazalboui* (*vivax*) is resistant to arsenic but susceptible to antimony ; nevertheless, they recommend the joint use of the two. Rodhain and collaborators succeeded in keeping two dogs alive in a thick fly belt by giving tartar emetic at critical times in the course of the infection. They found also that the drug in intravenous doses of 0·1 gram generally cures goats and sheep infected with *T. cazalboui* (*vivax*) but that a single injection given to mammals of the same species infected with *T. congolense* caused disappearance of the parasites from the circulation for from eight to ten days only.

Jones (1915) records the results obtained by the employment of tartar emetic in the treatment of *T. pecorum* infections in cattle in Portuguese East Africa. The observations were made on sixteen oxen, all of which showed high temperature and the general condition of all the animals was very poor and " some of them looked like dying within 48 hours." Intrajugular injections of from 1 to 2 grams of tartar emetic caused the disappearance of the trypanosomes in the course of four hours and the blood examination was negative for trypanosomes 24 hours and 5 days after the injection.

Yakimoff and Wassilewsky (1916) state that in the case of trypanosomiasis of camels in Russian Turkestan, emetic only acts when given in doses that are almost toxic. When administered in repeated small doses, the results were negative.

Van Saceghem and Nicolas (1916) observe that trypanosomes of the species *T. cazalboui*, *T. ugandæ*, and *T. congolense* disappear from the peripheral circulation within a few minutes after an intravenous, subcutaneous or intramuscular

injection of emetic, although the authors recognize the possibility that certain species of trypanosomes are resistant to the emetic treatment.

In view of the encouraging results reported by VAN SACEGHEM and other workers, ITURBE (1918) tested the efficacy of tartar emetic in the treatment of the trypanosomiasis of horses known in Venezuela by the name of *derrengadera*. The preliminary observations were made upon guinea-pigs experimentally infected with the disease. Doses of from 4 to 5 milligrams, administered intravenously or intramuscularly, caused the disappearance of the trypanosomes from the circulation within 15 minutes and the sterilization was maintained for several days, although some of the animals relapsed at later periods. The subsequent experiments were carried out on animals naturally affected with the disease. Five horses and two mules showing typical symptoms of the disease received intravenously every five days doses of from 1 to 1·5 grams of emetic and the results ensuing were very satisfactory.

HORNBY (1919) records having employed tartar emetic successfully in the treatment of infected oxen for transport purposes in fly-belts in Africa. The following three examples are illustrative of the general character of the results obtained by him :—

(1) May 14. Temp. 104° F. Gland juice and blood containing trypanosomes. Injected 60 c. c. of a 2 per cent. solution of tartar emetic intravenously.
May 24. Repeated injection.
June 24. Condition greatly improved.

(2) July 27. Blood shows a few *T. congolense*. Injected intravenously 60 c. c. of a 2 per cent. solution of tartar emetic.
August 8. Animal stronger. Injected 75 c. c. of a 2 per cent. solution of tartar emetic.
Nov. 14. Has been working steadily for 3 months.
Jan. 18. Animal in good condition.

(3) July 25. Blood contains a few *T. vivax*. Injected intravenously 60 c. c. of a 2 per cent. solution of tartar emetic.
Jan. 18. Blood negative, condition fair.

HORNBY regards tartar emetic as the most valuable drug yet tried in the treatment of *T. congolense* infection in cattle, and in a recent (1925) paper remarks, " Of the few drugs which are known to be of value in the treatment of this form of trypanosomiasis, tartar emetic stands alone at present, but the results obtained with it are not good enough to allow relaxation of search for a better." Although the employment of tartar emetic in the treatment of bovine trypanosomiasis would thus appear to have yielded a certain measure of success, the author's efforts to cure equine trypanosomiasis resulted in complete failure. During 1917 and 1918, he treated more than 200 horses and mules and also a few asses. Several of these animals harboured *T. brucei*, *T. congolense*, or both. He remarks that until some better method is known it is worth while injecting mules every five days, with 25 c. c. of a 4 per

cent. solution of tartar emetic, whilst they are in a fly-belt. This treatment will not prevent their contracting infection, but it will check fever and conserve energy. "It is, however, palliative, not prophylactic." The following three examples are illustrative of the general character of the results obtained by HORNBY in the treatment of equine trypanosomiasis :—

(1) A donkey infected with *T. congolense* received an intranvenous injection of 30 c. c. of a 2 per cent. solution of tartar emetic. Trypanosomes were present in the circulation 13 days later.

(2) A donkey received a single intravenous injection of 50 c. c. of a camphorated oily 2 per cent. suspension of tartar emetic. Parasites reappeared 16 days later.

(3) A mule infected with both *T. congolense* and *T. vivax* relapsed to both species after receiving three intravenous injections of 60 c. c. each of a 2·5 per cent. suspension of tartar emetic.

In a very recent paper, HORNBY and BURNS (1926) describe an attempt to keep oxen alive in Tanganyika Territory in a fly-belt where the animals were continuously exposed to infection with *T. congolense* and *T. vivax*. By means of fortnightly injections of tartar emetic they succeeded in keeping alive the greater number of the cattle so treated, which would have otherwise succumbed, as judged by the incidence of mortality in a control, untreated lot ; further, no advantage was derived by adding "Bayer 205" to the tartar emetic in treatment, as shown by the number of survivals in another lot treated in this manner. The treatment did not prevent infection, but caused the animals to remain in a useful condition.

ALDIGÉ (1920), in French Guinea, records having obtained encouraging results with tartar emetic, used alone or in conjunction with orpiment, in the treatment of trypanosomiasis of the pig (probably due to trypanosomes of the *brucei-pecaudi* group). The emetic was used in doses of 0·1 gram.

In combating an outbreak of trypanosomiasis among the large herds of cattle in Ruanda (Belgian Congo) VAN SACEGHEM (1921) treated the infected animals with a 4 per cent. solution of tartar emetic made in distilled water to which had been added 4 per cent. of chemically pure sodium chloride.

SERGENT, DONATIEN, and LHERITIER (1921) conducted a series of experiments on the action of tartar emetic upon dromedaries affected with debab. The preliminary experiments indicated that doses above 1·5 gram were liable to kill a dromedary weighing 300 kilos in less than 24 hours ; doses of 1 gram and below were well tolerated. One gram caused the trypanosomes to disappear from the blood and a lowering of temperature for eight days, whilst with 1·5 gram the effect lasted for ten days. In view of the fact that the trypanosomes reappeared within an average period of eight days after the injection of 1 gram of tartar emetic, a series of weekly injections of the drug seemed indicated and experiments on these lines conducted on nine dromedaries, artificially infected with debab, yielded results which may be regarded as having been generally satisfactory. The authors remark that the most

striking symptoms of debab in the case of females is the constant occurrence of abortion during the acute phase of the disease, whilst the most noticeable sign of recovery in the females treated with tartar emetic is the normal accomplishment of gestation.

CURSON (1923) recommends the employment of tartar emetic in a concentration of 1 gram to 20 c. c. of sterile normal salt solution for the treatment of nagana, the dosages being 1·5 grams for adult cattle, horses, donkeys, and mules, and 0·1 gram to 0·125 gram for dogs weighing 25 lb. As a routine measure five intravenous injections are recommended.

LEESE (1910), in India, tested the value of tartar emetic when used alone, in the treatment of 21 camels infected with surra, but the results were discouraging.

During recent years, a fairly extensive trial has been given by CROSS to tartar emetic as regards its efficacy in the treatment of surra in camels. In 1917, CROSS (1920) tested the efficacy of intravenous injections of tartar emetic upon six camels naturally affected with surra and the results obtained were encouraging. Again, during the cold weather of the year 1919-20, CROSS carried out a further series of experiments on a large scale and the conclusions arrived at by him, as briefly summarized in his Annual Report for that year, are as follows :—

(1) Ten doses of 60 c. c. of a 1 per cent. solution of tartar emetic given intravenously to full-grown camels do not effect a cure in the majority of cases.

(2) One large dose of 600 c. c. of a 1 per cent. soluton of tartar emetic given intravenously to full-grown camels does not effect a cure in the majority of cases.

(3) Ten to twelve doses of tartar emetic given on alternate days, commencing with 150 c. c. of a 1 per cent. solution and increasing to 300 c. c., gives considerable promise of success.

In a Bulletin published in 1922, CROSS and PATEL publish details concerning the procedure to be adopted in the treatment of camel surra by means of tartar emetic. The following doses are well tolerated and are reported to have given excellent results in camels of average size (a 1 per cent. solution was used and injections were given on alternate days) :—

	c. c.
1st day	50
3rd day	100
5th and 7th day	150
9th to 31st day	175
33rd and 35th day	200

The claims of tartar emetic to further exploration of its possibilities in the treatment of surra would therefore appear, from the observations recorded, to rank very high, and the method of treatment formulated by CROSS for camel surra must be regarded as registering a distinct therapeutic advance, particularly in view of the extensive and prolonged experience gained by this author in gauging its efficacy. One cannot but view with some apprehension the possibilities of the method findin

ready application in current field practice, on account of the necessity of repeating treatment (every alternate day) over a somewhat prolonged period (35 days), and although the relative cheapness of the drug employed commends itself for the treatment of the affected animals, the duration of the period over which skilled intervention is required (for, as is well known, the escape of tartar emetic into the perivascular tissues during intravenous injection is followed by severe local inflammation) constitutes a serious limiting factor to the propagation of the method in a country where treatment upon a large scale has to be undertaken. These limitations do not detract from the value of the method when applied in certain circumstances, as in mounted units with adequate veterinary staffs ;—if indeed, it were efficacious, if no more readily applicable and efficacious treatment were known, and if the cost of treatment compared with the estimated possibilities of success should render it an economically sound proposition. The subsequent discoveries concerning the properties of " Bayer 205 " make it possible that tartar emetic is now, in reality, not capable of fulfilling these conditions *vis-à-vis* surra in the more susceptible species of animals, and probably generally for infections due to the *brucei* group of typanosomes.

At the earliest stage of our experiments, therefore, before supplies of " Bayer 205 " became available, and, indeed, before it was felt that the introduction of this drug was likely to divert profitable channels of investigation elsewhere, supplies of tartar emetic were procured, for the testing of the properties of the drug alone, and in combination with arsenical compounds (notably tryparsamide, in view of the recent reports of success in its administration in human sleeping sickness) and bismuth compounds. It was believed that in the treatment of animals showing a high degree of susceptibility to surra, such as horses, combination with other drugs might resolve the problem of dealing with the supervention of " drug fastness," if the occurrence of this phenomenon should transpire to constitute the limitation to the sucessful administration of tartar emetic when applied alone. Initial experimentation upon equine subjects was, however, not considered economically warranted, on account of the likely small chances of survival of the experimental animals, and so therapeutic efforts were confined, in the first place, to buffaloes and hill cattle artificially infected with a strain of trypanosomes isolated from a natural outbreak among these animals, and which proved for some time to be intensely virulent, causing invariably death within a few days in inoculated cattle.

The minimum lethal dose of tartar emetic for cattle.

There are on record few indications as to the dosage of tartar emetic that can be employed with safety as a routine procedure in the treatment of trypanosome infections in cattle, and it appeared desirable to undertake a series of experiments to determine the lethal dose of the drug for these animals. A convenient form for use appeared to be an M-10 solution, representing 32·3 grams in a litre of water (the gram-molecular weight of potassium antimony tartrate being about 323 grams)

it was thought that there might be some advantage in exploiting the simpler trypanocidal compounds (tartar emetic, bismuth compounds) in this degree of solution, on account of a custom prevailing now largely among pharmacologists and experimental therapeutists to employ gram-molecular solutions of chemical compounds in their investigations.

The toxicity of an M-10 solution of tartar emetic for hill bulls on intravenous injection is shown in Table VII. It will be seen that doses higher than 0·3 c. c. per kilo body weight proved fatal in all cases, whilst of the three animals which received the drug at the rate of 0·3 c. c. only one succumbed. The minimum lethal dose for hill bulls was therefore taken as 0·3 c. c. of an M-10 solution per kilo body weight, or about 14 c. c. per 100 lb. body weight.

It will be mentioned later that in the course of subsequent experiments carried out on horses to estimate the value of a " saturation " treatment with tartar emetic, experiments were carried out on healthy horses in order to find out whether a cumulative toxic, or, on the other hand, a tolerance effect was set up in these animals by repeated daily intravenous administrations at certain dosages. Horses appeared to tolerate single dosages at the rate of 5 c.c and 10 c.c. M-10 solution per 100 lb. quite well, and on repeating the administration daily the 5 c.c. dosage could be borne for at least 17 days, whilst marked toxic symptoms were exhibited after the third day with the 10 c.c dosage.

Treatment of surra in buffaloes with M-10 solution of tartar emetic.

Following upon the preliminary indications obtained in regard to the dosage of tartar emetic that could be administered with safety, a series of controlled experiments were carried out with a view to testing the relative efficacy of graded doses of the drug administered to buffaloes experimentally infected with a strain of surra highly virulent for these animals.

Table VIII summarizes the protocols of 18 animals treated with an M-10 solution of tartar emetic at rates ranging from 1·25 to 5 c. c. intravenously per 100 lb. body weight. The results may be briefly indicated as follows :—

Dose of M/10 solution of tartar emetic per 100 lb. body weight	Number of animals tested	Number of deaths
5 c.c. . .	8	5 (37·5% survived).
2·5 c.c.	5	1 (80% survived).
1·25 c.c.	5	2 (60% survived).

It will be noted from the entries in the table also that in the case of a number of the recovered buffaloes trypanosomes appeared intermittently in the blood afterwards although the animals progressed to complete clinical recovery. The propor-

tion of recoveries following upon the single intervention does not appear in the above experiments to be very high, probably on account of the extraordinarily high virulence for the buffalo of the strain of trypanosome, which invariably produced a progressive septicæmia leading to death in the control animals.

However, further opportunity of estimating the effects of the drug was obtained in dealing with natural outbreaks of virulent surra among the buffalo stock at Muktesar. In one outbreak, the tartar emetic was administered during the septicæmia at the rate of 10 c. c. of an M-10 solution for 100 lb. body weight intravenously. Rather severe toxic symptoms appeared in some of the animals after this treatment resulting in death in a small proportion; the remainder were clinically cured. The routine practice of dealing with outbreaks was then laid down to consist of the administration of M-10 tartar emetic at the rate of 5 c. c. per 100 lb. The affected buffaloes have been invariably promptly "cured" by this treatment. In a few cases there has been a return of severe symptoms about three weeks after the treatment, but on repetition of the dosage at this stage the animals have again recovered and remained in a state of clinical recovery.

The fate of the trypanosomes after successful treatment in the buffaloes is one of much interest from the standpoint of comparative pathology. It would seem that in the bovine species the repression of virulent septicæmic invasion is not, probably never, followed by a sterilization of the host's system. Sometimes a further blood flush attracts attention by causing a relapse of clinical symptoms which necessitate a repetition of therapeutic treatment. The subsequent history, however, as revealed by daily examination of blood preparations, over several months, would appear usually to be that the trypanosomes return to the offensive intermittently, but with each return are beaten back with gradually increasing success by the host's own defensive powers until eventually the septicæmic invasions become less and less intense, with few trypanosomes discoverable in the blood preparations during the recurrences, and more and more spaced, by interva's of several weeks. It is hoped to publish the observations upon which these statements are made at length later.

In respect of furnishing information as to the parallel means of dealing efficaciously with equine surra, the results obtained with the bovine infection were only partially successful, inasmuch as the factor of natural host resistance to the parasitic attack varied greatly in the two species of animals; for, whereas the bovine organism was generally capable of dealing effectually by virtue of its own resources after repression of virulent invasion by therapeutic aid with attempts on the part of the parasites to regain the ascendency, and the parasites were reduced subsequently to a status approaching that of harmless commensals, in the equine species the host's own defences are not capable of becoming strengthened to a corresponding degree and, failing complete sterilization, progressive morbidity accompanies each recurrence of the trypanosomes in numbers in the blood stream. Hence, in the face of virulent bovine infection, the only information readily attainable con-

terns the trypanocidal properties of single administrations of the drugs tested, and such information is rather of a qualitative than of an quantitative kind.

Treatment of equine surra with tartar emetic.

In the course of our experiments upon the properties of tartar emetic towards surra in horses conducted subsequent to the study of the drug *vis-à-vis* bovine surra, the following basic information was acquired, the details concerning which may be obtained from the histories of the individual animals treated :—

(1) Healthy horses tolerate intravenous injections of the drug of approximately the same magnitude as recommended for cattle.

(2) Experiments upon the prophylactic treatment of horses against virulent surra infection indicates that, after intravenous administration of what was considered a full therapeutic dose, the drug remained in trypanocidal concentration in the blood stream for about 24 hours, but not longer.

(3) Hence, in order to maintain the circulation in a state inimical to the development of the trypanosomes, the therapeutic dose must be repeated daily, or, at any rate, on alternate days, during the period over which it is considered necessary to protect the animals from danger of relapse.

(4) Tartar emetic appears to exert a drastic, direct toxic action on the trypanosomes. When administered therefore in full therapeutic dose to a horse exhibiting a trypanosome septicæmia it is liable to cause sudden death of the animal, either from occlusion of the blood capillaries or liberation of toxic substances from the dead trypanosomes.

The last of the above statements is strikingly illustrated by the protocols of Horses 23, 47, and 58, all of which received the drug when trypanosomes were numerous in their blood. It is curious that alarming symptoms were not likewise so distinctly manifested when the drug was employed in large doses for the treatment of buffaloes infected with surra. The administration of 5 c. c. M-10 solution per 100 lb. body weight intravenously into the above horses, however, produced death in two cases before the process of injection was actually completed, and there would appear to be no doubt that a dose that can be safely tolerated by a non-infected horse is dangerous for a surra-infected horse.

In commencing the treatment of horses with tartar emetic it is obvious therefore that great care must be taken, and there would appear to be two possible methods of overcoming the dangers attendant upon the commencement of treatment with this drug: (*a*) To commence with very small doses, which should then be gradually increased in size in subsequent inoculations until the full tolerated therapeutic dose is reached (the method of treatment last recommended by Cross for camel surra is in accord with this notion); (*b*) To administer initially another trypanocidal agent which brings about a clearance of the circulation less drastically,

and then " follow up," as soon as the trypanosomes have disappeared, with a course of injections of tartar emetic administered in uniformly high therapeutic desage. For the purpose of this initial clearance we have used in our experiments " Bayer 205 " (in doses of 0·5 to 1 gram per 1,000 lb.) and tryparsamide.

It has been brought to our notice by our colleague Mr. T. F. Quirke, Chief Superintendent, Civil Veterinary Department, Punjab, in a personal communication, that treatment by means of what he terms a " saturation method " with tartar emetic has given him recently very encouraging results in dealing with cases of naturally contracted surra in the field. The system of treatment formulated by CROSS, and held by him to have given the greatest measure of success in the treatment of camel surra is indeed a " saturation method," and, according to the notions we have gained regarding the *rationale* of successful treatment in horses, is in accord with sound principles. The method would also find its analogy in the procedure adopted by HOLMES (1913), who employed atoxyl for the purpose of the initial clearance and " followed up " with arsenious acid administered in ball. The *rationale* of the system is explained by HOLMES thus : " Atoxyl has no curative effect, but exercises a rapid action in clearing the circulation of mature trypanosomes. It is therefore used only when trypanosomes are present in the circulation. The use is indicated at the commencement of the treatment.....Injection of atoxyl has to be followed by 10 doses of arsenious acid in ball."

It seems to us that a rational system of " saturation " should connote the maintenance in the blood stream of the therapeutic agent employed over a certain prolonged period in a definite state of concentration. This degree of concentration should (i) be such as will not produce a state of intoxication in the host from which it cannot make a good recovery ; (ii) be high enough to exert an undoubted parasiticidal effect upon any trypanosomes that find ingress into the blood stream during the period of treatment ; and (iii) not be allowed to become depressed during the period so as to persist in distinctly sub-lethal quantities, which condition is generally understood to mitigate the activity of the drug by the acquisition of the property of " drug-fastness " on the part of the trypanosomes. In the case of " Bayer 205," it has already been noticed that a state of " saturation " of the blood stream is maintained for a period extending over a month after the administration intravenously of a single full therapeutic dose of the drug, and the drug appears to possess this property in virtue of its slow excretion, which again may be held to denote very low diffusibility or penetrability, and to be probably a function of the large molecular constitution of the preparation. Tryparsamide, as will be noted in the section dealing with this drug, represents the antithesis of such properties, as it appears to be characterized by extremely high diffusibility and liability to excretion.

It is generally agreed by workers that tartar emetic is a drug possessing low penetrative powers, as is exemplified by the following illustrative references.

VAN SACEGHEM and NICOLAS (1916) refer to the very limited powers of penetration possessed by tartar emetic, on account of which such trypanosomes as have

lodged themselves in the deeper tissues escape the action of the drug. They further point out that such trypanosomes are generally those that have a tendency to infiltrate into the deeper parts and resist the therapeutic action of the drug, eventually producing relapses.

MASTERS (1918), from observations made on 370 cases of human trypanosomiasis in the Belgian Congo, concludes that although tartar emetic has often proved efficacious in clearing up the symptoms and trypanosomes when all other remedies have failed, the penetrating action of the drug is insufficient to kill trypanosomes in the deeper tissues, and further, that the drug disappears quickly from the peripheral circulation, or becomes rapidly transformed locally and excreted.

According to LEFROU (1923), the injection of tartar emetic does not diminish the meningeal reaction in human trypanosomiasis; on the contrary, it tends to increase such reaction and he illustrates this by means of a table wherein he summarizes the protocols of six patients treated with the drug.

The view expressed by some authors that the drug is characterized both by lack of penetrability and liability to rapid excretion would seem to be paradoxical, unless the substance undergoes rapid transformation in the blood into something which is inert or readily excreted. Hence, it was thought desirable to obtain precise knowledge as to the duration of retention of the drug in the circulatory system in trypanocidal concentration after intravenous administration of the drug in full therapeutic dosage. The experiments dealing with the solution of this problem are dealt with again later in the section dealing with the prophylactic action of tartar emetic, but it may be stated here that they proved the drug was retained in manifest trypanocidal concentration for 24 hours after intravenous inoculation of a full dose, as evidenced by the inability of trypanosomes to gain a foothold in the horse's system when introduced in virulent blood subcutaneously at this interva lafter the drug injection. The period of retention would, therefore, appear to be a relatively long one when compared with that of a drug like tryparsamide, which failed to prevent the establishment of the trypanosomes in the system even when administered intravenously simultaneously with the subcutaneous injection of trypanosomes. On the other hand, it was a very short one in comparison with that observed to occur with a full dose of " Bayer 205."

In the *rationale* of " saturation " it would therefore seem necessary to repeat the intravenous injection of an adequate dose of tartar emetic every 24 hours, or at any rate, on alternate days for a prolonged period. Preliminary experiments (see protocol of Horse 23) showed that a healthy horse could tolerate the repeated injection of the drug in dosages of 5 c. c. of M-10 solution per 100 lb. body weight for at least 17 injections.

With this knowledge available a few tests were then made of the " saturation " system, which although small in number are considered to be sufficiently illustrative of the prospects of success. Table IX summarizes the records of four horses treated with tartar emetic after initial clearance of trypanosomes with " Bayer

205 " (small doses) or tryparsamide. Success was obtained in only one out of the four horses.

One case (Horse 53) is of particular interest. The horse had become much debilitated as the result of infection, and after repression of the trypanosomes in the blood stream with small dosages of " Bayer 205," was treated every 3 days with the therapeutic dose of tartar emetic. After the fourth injection it developed signs of cerebral disease, and two days after the fifth injection it succumbed suddenly. No trypanosomes appeared in the blood stream during the treatment, but they were discoverable after death in considerable numbers in the cerebro-spinal fluid ; no trypanosomes could be found in the centrifuged deposits of fluids from the peritoneal, pleural, or pericardial sacs.

Horse 54, after having a " clearing " injection of "Bayer 205 " (0·5 gram per 1,000 lb.), was given three injections of tartar emetic at two-day intervals ; it relapsed later, developed most pronounced symptoms of paraplegia, and was destroyed *in extremis* 17 days after the last tartar emetic injection ; trypanosomes were discovered in large numbers in the centrifuged cerebro-spinal fluid.

Horses 48 and 51 received initial treatment with tryparsamide followed by multiple repeated injections with tartar emetic. Horse 48, which received 10 injections at three-day intervals, relapsed 13 days and died in 33 days after the cessation of the treatment ; trypanosomes were discoverable in the cerebro-spinal fluid on examination 13 days after the end of treatment and were numerous at the time of death. Horse 51, on the other hand, never relapsed and was discharged in excellent condition 437 days afterwards (*i.e.*, on 16th December 1926). This horse in the first place received three injections of tartar emetic on alternate days after the tryparsamide. This course of treatment was not sufficient to prevent a relapse, and so it was repeated with 10 injections on alternate days following upon tryparsamide ; no trypanosomes were found in cerebro-spinal fluid when examined after the 6th and last injections. It is not improbable that the course of the infection in this animal was largely determined by the fact that drug intervention occurred at a relatively early stage of the disease, whilst the inoculation of tryparsamide simultaneously with the virulent blood (for the purpose of another experiment) must be regarded as a factor that possibly contributed to the recovery of the animal by having caused an initial lowering in the virulence of the organisms.

It might be assumed that a " saturation " treatment with tartar emetic is susceptible of bringing about a lasting cure when the infected horse is brought under treatment early and is in good bodily condition ; at a more advanced stage, the treatment is likely to be followed by a relapse, or cerebro-spinal involvement, while, when the animal has become depressed in vitality by the progress of the disease or otherwise, the intensity of the treatment is likely to prove more than the animal can withstand.

During recent years, a method that has found favour with a section of workers in the treatment of animal trypanosomiasis is to use the drug in conjunction with

" Bayer 205." In fact, tartar emetic has long been generally regarded as a drug eminently suitable for combination with other medicaments. As BLANCHARD and LAIGRET (1924) remark, few workers have employed tartar emetic alone in the treatment of trypanosomiasis, and the fact that the drug has almost always been used in association with atoxyl indicates that full reliance is not placed on the efficacy of tartar emetic alone.

BERG (1925), working for the Bayer firm on nagana in South Africa, concludes, from what would appear to be a very small number of observations, that treatment with " Bayer 205 " is greatly enhanced in value by combination with tartar emetic. Cattle exposed to the bites of tsetse flies on a farm in Zululand during a period of 14 days remained free from infection when treated concurrently with " Bayer 205" and tartar emetic in doses of 2·5 grams and 1 gram, respectively. In cases of naturally contracted *T. congolense* infection, cure was effected by means of five 4-gram doses of " Bayer 205 " combined with 1-gram doses of tartar emetic, whilst four 2-gram doses of " Bayer 205 " combined with 1-gram doses of tartar emetic sufficed for the treatment of *T. brucei* infection. It has been mentioned in an earlier reference that HORNBY and BURNS (1926) have failed to demonstrate any advantage in combining the two drugs in the treatment of cattle exposed to infection in a fly-belt.

We can see no adequate *a priori* reason for believing that combination with tartar emetic is likely to enhance markedly the curative properties of " Bayer 205." As stated in the sections dealing with the properties of this latter drug, one of its essential limitations is its lack of diffusibility, which renders it incapable of penetrating the endothelium of the blood vessels into the remote tissues and spaces in which there may be lurking trypanosomes. This defect is one which characterizes largely tartar emetic as a trypanocidal agent. It would be readily conceded that there might be obvious advantage in combining " Bayer 205 " with a very diffusible agent such as tryparsamide, and thus combating the development of cerebro-spinal involvement liable to ensue with the intravenous administration of " Bayer 205 " alone. It has been stated, however, that this serious limitation in the therapeutic properties of " Bayer 205 " may be overcome in a more direct manner, by its concurrent administration in proportionate amount intrathecally. However, without having performed any experiments directly upon the value of the combined " Bayer 205 "—tartar emetic treatment, we are unable to express definitive opinions regarding its merits.

In order to combat the tendency to cerebro-spinal involvement with the tartar emetic treatment, we have already submitted on request advice to field workers as to an appropriate dosage of this drug for concurrent intrathecal administration, namely, for horses (or camels) about 30 c.c. of a 0·1 per cent. solution per 1,000 lb. body weight (calculated arithmetically on the assumption that the quantity required for the cerebro-spinal tissues is about one-fivehundredth of that which represents a full therapeutic dose for intravenous injection).

There would appear to be manifested, on the part of certain individuals, an idiosyncrasy towards the effects of tartar emetic. In regard to the action of the drug on human beings, CHRISTOPHERSON and GLOYNE (1926) observe that patients subjected to a prolonged course of intravenous injections of antimony frequently exhibit signs of hypersensitivity—presumably an example of drug allergy—with non-toxic doses. The authors suggest that the hypersensitivity may be due to an alteration of protein metabolism.

The prophylactic action of tartar emetic.

Table X summarizes the records of 7 horses treated prophylactically with varying doses of tartar emetic. It will be seen that infection was resisted completely only in two (Horse 35 and Horse 45) in which the animals received single or repeated doses of the drug at the rate of 10 c.c. of a 3 per cent. (nearly M-10) solution per 100 lb. body weight, simultaneously with or a day previous to the infective inoculation with highly virulent blood subcutaneously. Five c.c. of the solution given at the same rate did not prevent infection arising from the virulent inoculation administered a day later, although the infection appeared to be distinctly mitigated at its commencement, in comparison with the degree of infection that occurred in the horses inoculated with trypanosomes at later intervals and in the control horse. In this connection, it must be borne in mind that the trypanocidal activity of the drug would probably have to be sustained for a period considerably longer than that represented by the interval between the prophylactic intravenous inoculation of the drug and the subsequent subcutaneous virulent inoculation, for the capacity of the trypanosomes introduced subcutaneously to set up systemic invasion may be prolonged for some time after their introduction under the skin.

IV. TREATMENT OF SURRA WITH TRYPARSAMIDE.

Tryparsamide, or the sodium salt of N-phenylglycineamide-p-arsonic-acid, was first made by JACOBS and HEIDELBERGER in 1915 and later studied biologically by PEARCE and BROWN (1921) of the Rockefeller Institute. In the course of these investigations it was brought out that, as a remedy for experimental trypanosomiasis in small animals, the drug was in many respects superior to the other arsenical compounds chemically somewhat similarly constituted, atoxyl, arsenophenylglycine and salvarsan. These biological experiments indicated that the drug merited trial as to its efficacy in the treatment of human trypanosomiasis and consequently in May 1920, Miss PEARCE was sent by the Rockefeller Institute to the Belgian Congo to study its therapeutic value in the treatment of human sleeping sickness; her report, which is based on observations made on 77 cases, was published in December 1921. The results, as summarized by her, may be briefly indicated as follows:—

Tryparsamide was found to possess a marked trypanocidal activity in human trypanosomiasis caused by *T. gambiense*. Single doses of from 0·5 to 5 grams pro-

duced a sterilization of lymph glands and blood in an average period of 6 to 12 hours. The duration of peripheral sterilization following single doses of 9 to 83 mg. per kilo ranged from 17 to 111 days, and in some of the cases no relapse was detected during the post-treatment observation periods.

The most noticeable feature of the results recorded by Miss PEARCE would appear to be that relatively few doses of the drug produced in advanced cases a rapid diminution of the cells of the spinal fluid, and this was followed by a definite improvement of mental and nervous symptoms. If these observations should be borne out by future experience, the application of tryparsamide must be regarded as having registered a definite advance in the therapy of trypanosomiasis, inasmuch as the cerebro-spinal involvement constitutes a phase of the disease that has hitherto been generally regarded as resistent to practically all forms of curative treatment.*

Since the publication of PEARCE's early work, several other workers have referred to the value of tryparsamide as a drug possessing remarkable power of tissue penetrability.

CHESTERMAN (1923, 1924) gives the history of 37 cases of sleeping sickness treated with tryparsamide in the Belgian Congo. The work was undertaken mainly to test the results of repeated administration of large doses at weekly intervals by the intravenous route, with the object of rendering normal the cell content of the cerebro-spinal fluid of the most advanced cases. In summarizing the results, the author states that 15 out of the 37 patients remained well during an average observation period of over two years from the end of a single course of treatment. All the patients had exhibited symptoms of involvement of the central nervous system, as confirmed by an average cell content of 630 cells per c.mm. ; whilst in six of these cases the presence of trypanosomes was detected. Two or three of these " were unable to walk, one was incontinent, and all long had passed the stage when there is any hope to be entertained of a cure by atoxyl and other drugs." The author believes that failures in many instances are attributable to faulty dosage and expresses the conviction that " the curative power of tryparsamide is superior to that of ' Bayer 205.' "

LETOUTURIER, DE MARQUEISSAC, and JAMOT (1924) record a series of observations made on 14 patients representing practically all stages of human trypanosomiasis, treated by means of tryparsamide, in the Cameroons. In discussing the results, the authors refer to the efficacy of the drug for patients in the second stage of the disease, showing symptoms of involvement of the nervous system and remark that they are not aware of any other trypanocidal agent possessing such remarkable power of penetrating the meninges.

* On the other hand, LEFROU and OUZILLEAU (1922) observe that the action of tryparsamide is only analogous to that of atoxyl and neosalvarsan : a series of injections may cause a diminution of lymphocytosis and a slight variation in the quantity of albumen which coincide with a clinical amelioration, but these changes are only transitory ; the lymphocytosis and the albumen increase and the disease runs its course.

YORKE (1925), after a careful analysis of the results recorded by various workers, concludes as follows in regard to the relative value of "Bayer 205" and tryparsamide in the treatment of human trypanosomiasis :—

> "The general conclusions appear to be that, apart from its peripheral sterilising action and the immediate physical improvement which it produces, 'Bayer 205' is useless in advanced cases of either *T. gambiense* or *T. rhodesiense* infections, in so far as it has no action on the cerebro-spinal infections and the disease proceeds to a fatal issue. For this class of case tryparsamide should undoubtedly be employed."

As to the value of tryparsamide as a remedy for trypanosomiasis in animals, the application of the drug would seem to have been hitherto mainly confined to certain cases of mal de caderas.

SMILLIE (1923), who tested the efficacy of the drug upon a number of horses affected with this disease in Brazil, concludes as follows :—

1. Single doses of tryparsamide of from 5 to 8 grams given intravenously to horses and mules suffering from mal de caderas were followed by a marked reduction in the number of parasites in the circulating blood. In addition there was a prompt cessation of fever.
2. The administration of two doses of 8 grams, separated by an interval of three weeks, was highly effective.
3. The administration of tryparsamide was not followed by any toxic symptoms or other evidence of constitutional injury.
4. The treatment of animals in the last stages offers only a problematical measure of success.

In a communication addressed to the writer, Dr. Louise PEARCE (1922) writes as follows :—

"During the past winter in South America, about 100 horses affected with caderas were treated with tryparsamide. The results were on the whole satisfactory. From 1 to 3 doses were given intravenously, the size of the individual dose ranging from 2 to 3 grams. On one occasion, a dose of 6 grams was followed by one of 10 grams on the following day, the weight of the horse being in this instance 700 lb. The drug was given intravenously in most instances. There was very prompt physical improvement and disappearance of trypanosomes in the circulating blood and no untoward effects were observed. Our last reports on this work came in the late spring so that we cannot state whether these horses were cured or the infection merely kept under control for a certain time. From the economic point of view, however, the result of the treatment is very encouraging."

In a very recent paper HORNBY (1925) published a series of observations relative to the efficacy of tryparsamide in the treatment of cattle naturally or artificially infected with *T. congolense*.

The protocols of the animals treated are summarized below :—

1. Young cow 3 years old, infection naturally contracted. Injected intravenously with a single dose of 10 grams of tryparsamide dissolved in 100 c.c. of water ; no visible ill-effects following injection. On the 4th day after treatment no parasites observable in blood smears, but on 6th day parasites re-appeared. Animal unable to rise and destroyed.

2. Ox in good condition.

Aug. 15. Artificially infected with *T. congolense.*—Aug. 23. Trypanosomes appeared in circulation.—Aug. 24. Administered intravenously 20 grams of tryparsamide in 80 c.c. of water ; no visible ill-effects following injection.—Aug. 25 and 26. Temperature normal, but trypanosomes present in small numbers.—Aug. 27. Trypanosomes absent.—Aug. 28. Parasites re-appeared in blood stream.—Aug. 29. Parasites swarmed and " presented the unusual picture of many undergoing *multiple fission.*" Administration of two successive doses of 30 c.c. of a 4 per cent. solution of tartar emetic cleared circulation.—Sept. 1. Animal died. (Cerebro-spinal fluid clear.)

3. Ox, 3 years old.

May 16. Artificially infected with *T. congolense.* The subsequent infection was not alleviated by a full course of tartar emetic treatment, as trypanosomes reappeared 28 days after the last injection.—Aug. 14-17. Daily intravenous injection of 10 grams of tryparsamide in 40 c.c. of water.—Aug. 18. Intravenous injection of 5 grams of tryparsamide ; no toxic effects following injection.—Aug. 21. Blood showed small numbers of trypanosomes. Animal observed staggering. Destroyed.

4. Young ox.

Aug. 5. Artificially infected with *T. congolense.* Aug. 14. Trypanosomes appeared in circulation. Aug. 15-19. Daily intravenous injection of 10 grams of tryparsamide in 40 c.c of water.—Aug. 23. Trypanosomes swarmed. Aug. 24. Trypanosomes presented appearance of multiple fission. Course of tartar emetic treatment commenced. Animal considered as cured at time of writing.

From the above observations, the author concludes : " When given to cattle infected with *T. congolense*, tryparsamide has no beneficial effect, but, on the contrary, appears to make the blood extraordinarily favourable for multiplication of the parasites."

It would therefore seem that tryparsamide is incapable of acting as efficaciously upon infections due to the *congolense-dimorphon* group of trypanosomes as it acts, according to the published reports, upon infections due to the *brucei* group.

In the course of the series of experiments undertaken by us at the Muktesar Laboratory, the efficacy of tryparsamide was tested on buffaloes and horses experimentally infected with surra and also on two natural cases of equine surra. Samples of the drug were also distributed to veterinary colleagues in the field for

trial, but as the reports forthcoming are in agreement with the results obtained at the laboratory they are not discussed in this paper.

Treatment of surra in buffaloes with tryparsamide.

Table XI summarizes the protocols of 17 buffaloes experimentally infected with a strain of surra highly virulent for these animals and treated at the height of infection with doses, ranging from 0·5 to 0·05 gram per kilo body weight, of tryparsamide administered in 10 per cent. aqueous solution intravenously. The results may be briefly indicated as follows :—

Dose per kilo	Number of animals treated	Number of deaths
0·5 gram . . .	3	3 (100 per cent.)
0·25 „ . . .	3	3 (100 „)
0·2 „ . . .	3	3 (100 „)
0·125 „ . . .	2	1 (50 „)
0·1 „ . . .	3	1 (33·3 „)
0·05 „ (2 doses) . .	3	0

The results seemed to indicate that a large proportion of the animals succumbed to the toxic effect of the drug, although this mortality had not been anticipated, inasmuch as the dosages employed were considerably below what had been determined by PEARCE and BROWN (1919) as the minimum lethal dose for rabbits, namely, 0·7 to 0·9 gram per kilo. At the same time, it was recognized that, as emphasized later by KLEINE (1924) in the case of " Bayer 205," very erroneous results were likely to be obtained if one calculated the dosage to be used in one kind of animal from that obtained in the case of another species.

A short series of experiments with a 10 per cent. solution of tryparsamide was therefore undertaken to determine the minimum lethal dose of the drug for buffaloes and hill bulls. From the results which are summarized in Table XII, it will be seen that doses above 0·2 gram per kilo body weight proved fatal in all cases, whilst one out of the four injected at the rate of 0·2 gram per kilo succumbed. The experiments had to be suspended, unfortunately, at this stage owing to the limited supplies available of the drug, and when further supplies came to hand the virulent buffalo strain of trypanosome had become suddenly attenuated so that experimentation on cattle concerning the efficacy of the drug could not be properly carried out.

From the results recorded in the case of the buffaloes mentioned above, that received a highly virulent surra infection and survived after treatment with tryparsamide, and from the results derived from a subsequent series of tests in which the strain of surra employed proved to have become so much degraded in virulence that it did not kill even the control animals, it became apparent that the intraven-

ous administration of tryparsamide in what was found to be the maximum tolerated therapeutic dose did not bring about a complete sterilization of the system, although a clinical "cure" was effected with virulent infection. The trypanosomes persisted subsequently and re-appeared intermittently in the blood stream, but not to the extent of endangering the life of the animal as they did before their activity was checked by the administration of the drug. It would therefore seem that the effects of tryparsamide upon the cattle infection were parallel to those of tartar emetic.

Treatment of equine surra with tryparsamide.

The effects of the drug in the treatment of equine surra are illustrated by those obtained in the case of two horses that had contracted infection naturally at our branch laboratory at Bareilly. These tests represent the earliest of our experiments in treatment (see charts of Pony 174 and "Ekka" Pony Mare). One of the horses was administered 3-gram doses of the drug, in 10 per cent. solution, intravenously, repeated at three-day intervals, and the other received the drug in the same manner at seven-day intervals. In both cases the treatment was unsuccessful; in the first case the failure might be attributed to the dose being too small, and in the second case the course of the infection indicated that the parasites had become tryparsamide-fast. The indications furnished by these preliminary tests were subsequently fully borne out by the results of more precise experiments upon artificially infected horses at Muktesar, and by reports from the field.

In one respect, however, tryparsamide possesses a considerable virtue which is analogous to that displayed by "Bayer 205." When it is administered in the treatment of animals having numbers of trypanosomes in their peripheral blood, the maximum safe dose for a healthy animal (0·2 gram per kilo body weight in a 10 per cent. solution) may be given with safety to the infected animal intravenously, and the trypanosomes then take several hours to disappear from the circulation, so that there is no danger from occlusion of the capillaries or liberation of toxic decomposition products as in the case of tartar emetic. This point is illustrated in the case of Horse 51 (see chart, Plate V; 22-8-1925), which showed trypanosomes in its blood till the fifth hour after treatment, while the result of blood examination made at the sixth hour was negative.

Nevertheless, as is illustrated by the course of infection and treatment in the case of one of the horses that had contracted infection naturally, the disappearance of the trypanosomes after a massive intravenous injection only lasts a few days, and when the administration of the drug is repeated at each subsequent relapse the trypanosomes, after each disappearance, re-appear at progressively shorter intervals.

The duration of retention of the drug in trypanocidal concentration in the system after massive intravenous inoculation is, as measured by its prophylactic action,

relatively ephemeral, for administration at the rate of 0·2 c.c. of a 10 per cent. solution per kilo intravenously did not prevent infection when virulent blood was given simultaneously subcutaneously.

It will be noted from the protocols attached to this paper that in the case of some infected horses (Nos. 68 and 70) an attempt has been made to estimate the value of tryparsamide administered intrathecally in appropriate dosage concurrently with the administration of "Bayer 205" intravenously; it was believed that in view of its reported powers of tissue penetrability and its use by some medical workers in this manner in the treatment of human syphilis, it might perhaps display some superior value as a medicament for administration by the intrathecal route.

However, the results of our experiments have forced us to conclude that tryparsamide is of extremely limited value in the treatment of equine surra (see protocol of Horse 51), whether judged by the permanence of its therapeutic effect as expressed by the duration of peripheral sterilization, or by its power of tissue penetrability, as measured by the extent to which it is capable of arresting the active progression of the disease towards cerebro-spinal involvement, whilst its prophylactic action is also negligible. Its action seems to us to resemble that described for atoxyl *vis-à-vis* equine surra.

V. Treatment of Surra with Bismuth Compounds.

The therapeutic use of the compounds of bismuth has hitherto been practically restricted to the treatment of spirochætal infections. In the treatment of syphilis, the action of bismuth has been found to be even superior to that of mercury (Sazerac and Levaditi, 1922), and although the administration of bismuth has sometimes been followed by an impregnation of the buccal mucous membrane with the drug (as evidenced by blueness of the tongue and other symptoms), no disturbing toxic symptoms have resulted (Fournier and Guenot, 1922).

On the other hand, the compounds of bismuth would appear to have been tried with only partial or no success in the treatment of trypanosomiasis.

Frouin and Guillaumie (1921) tested the action of bismuth subnitrate upon mice experimentally infected with nagana and obtained what would appear to be only partial success. However, when employed alone or in conjunction with the salts of cerium or yttrium, the drug caused the disappearance of the trypanosomes for some time and a prolongation of the life of the animals.

The efficacy of bismuth in the form of soluble bismuth sodium tartrate (which was also one of the two compounds of bismuth employed in the course of the experiments recorded in this paper) was tested by Adler (1921) for small animals experimentally infected with *T. rhodesiense* and *T. brucei* (nagana ferox). The minimum lethal dose was found to be 0·047 gram for mice and 0·062 gram for guinea-pigs.

When administered to infected animals the drug caused only a temporary disappearance of the parasites.

A compound which has had a relatively wide application in the treatment of trypanosomiasis is the tartro-bismuthate of sodium and potassium, also known by the name of " trépol."

VLADESCO and IRIMINOIU (1923) studied the action of trépol upon guinea-pigs experimentally infected with *T. equiperdum*, nagana, and surra. Administered intraperitoneally, the drug caused an almost immediate disappearance of the trypanosomes, but the animals died of peritonitis. Intramuscular and subcutaneous injection of the drug was followed by a disappearance of the parasites, but relapses occurred in 16-33 days.

In view of the highly encouraging results obtained with bismuth compounds in the treatment of syphilis, VAN SACEGHEM (1923) tested the efficacy of bismuth hydroxide and tartro-bismuthate of potassium and sodium in the treatment of cattle infected with *T. congolense-pecorum* var. *ruandae*, but the results were very unsatisfactory. Intramuscular administration of 10 c.c. of a 50 per cent. suspension of bismuth hydroxide failed to clear the blood of trypanosomes, whilst intravenous injection of tartro-bismuthate of potassium and sodium, in doses of 5 and 2 grams dissolved in water, produced fatal results within a few minutes after application. Treatment with progressive doses of 0·5, 1, and 1·5 grams administered intravenously or intramuscularly, or subcutaneous administration of 10 c.c. of a 50 per cent. suspension of the tarto-bismuthate in olive oil, had no effect on the trypanosomes.

In regard to the efficacy of the sodium-potassium salt for human trypanosomiasis, VAN DEN BRANDEN and VAN HOOF (1922), who tested the action of the drug upon three patients, observe : " The salt does not appear to possess any real trypanocidal property. Like the salts of mercury which are very effective against the spirochætes causing syphilis but are without any action upon *T. gambiense* infection, the salts of bismuth are very energetic spirochæticides but do not appear to be effective against *T. gambiense*."

Treatment of surra in cattle with bismuth.

In our earlier experiments, a fairly considerable number of tests were made (which are not reported upon at length in this paper but will form part of the text of a subsequent publication) upon the possibilities of one of the simpler bismuth compounds against virulent surra infection in cattle. Bismuth phosphate was selected for this purpose, and as this substance is insoluble in water and readily deposited from an aqueous suspension, it was finally settled that for intravenous administration a suitable menstruum consisted of an 8 per cent. solution of gum arabic prepared in the cold. Finely pulverized bismuth phosphate was added to the gum solution, until it was present in the equivalent of an M-10 concentration. Healthy buffaloes tolerated large dosages of the emulsion intravenously ; in tests

conducted simultaneously with those mentioned in the same connection with tartar emetic and tryparsamide upon infected buffaloes it was found that the gum suspension of bismuth phosphate was sufficiently trypanocidal in effect to stay the progress of virulent attack and to bring about clinical " cure," but the trypanosomes persisted subsequently in a subdued condition of activity in the hosts' systems.

It would therefore appear that the insoluble bismuth salt possessed a distinct trypanocidal action, rising to a practically useful degree in the case of the bovine affection. Although it might not possess any advantages over the antimony salt, tartar emetic, except in regard to its very much smaller local irritant effect, it had in common with this compound the important merit of relative cheapness, and it was thought that it might possibly be a useful subsidiary agent for alternation in a combined treatment with the tartar emetic in dealing with the more difficult problem of equine surra. Further, it might transpire that on " saturation " of the system with the more insoluble element a lasting condition inimical to the development of the trypanosomes could be set up.

Treatment of surra in horses with bismuth.

Curiously, intravenous administration to healthy horses of the gum suspension of bismuth phosphate in dosages equal to or smaller than those which had been tolerated quite safely by the infected buffaloes, and had produced the therapeutic action in these animals, rapidly caused death in the horses. On further investigation, it transpired that this toxic effect was attributable, not to the insoluble suspended bismuth salt, but to the gum solution itself. It was proved that horses were very susceptible to the action of small quantities of gum solution injected intravenously, so that adequate quantities of the bismuth salt could not be suspended in that menstruum for treatment. It was then resolved to test the possibilities of devising some other harmless fluid with the requisite degree of viscosity to maintain the heavy powder in suspension for a sufficient time for intravenous injection into horses, and after some trials it was found that a strong aqueous solution of glucose (50 per cent.) was suitable. The glucose solution alone had no appreciable toxic action when given in the quantities required for the tests. Tables XIV and XV represent some tests carried out upon horses in order to determine the lethal effect of intravenous administration of the suspension of the insoluble salt and of the soluble bismuth sodium tartrate.

Table XVI summarizes the records of four horses which were treated prophylactically with the two salts. As regards bismuth phosphate, it will be seen that the administration of 5 c.c. per 100 lb. body weight of a 25 per cent. suspension did not prevent infection when virulent blood was injected simultaneously subcutaneously, whilst an attempted " saturation " of the system by daily inoculations of the drug at half the above rate for 10 days did not modify appreciably the intensity of the infection that developed when the virulent infection was applied a day after

the cessation of the prophylactic injections. The hope that the insoluble salt would prove capable of relatively prolonged retention in trypanocidal concentration therefore was groundless. In the case of the soluble salt, the administration of ten successive doses at the rate of 1 c. c. of a 4 per cent. solution per 100 lb. body weight —the maximum as disclosed by the tests on toxicity that could be safely tolerated— failed to modify the intensity of the infection that developed when virulent blood was injected subcutaneously a day after the cessation of the prophylactic treatment.

The therapeutic effect of bismuth sodium tartrate was tested in only one instance (Horse 23), in which the infected animal was treated 17 days after the infective inoculation, with three successive doses of a 4 per cent. solution of this salt at the rate of 1 c. c. per 100 lb. body weight. The drug had no appreciable action upon the trypanosomes, and the animal succumbed 2 days after the cessation of treatment.

No experiments were conducted upon the therapeutic value of bismuth phosphate upon horses, as in view of the preliminary indications obtained it was not considered profitable to proceed far in the exploitation of these compounds.

VI. Summary and Conclusions.

The work in progress upon the chemotherapy of trypanosomiasis, due to *Trypanosoma evansi*, would appear to warrant the following conclusions :—

A. Bovines.

Outbreaks of surra in cattle, including buffaloes, which occasionally occur in India (with high mortality particularly among buffaloes) are easily checked by the administration of injections intravenously of relatively simple trypanocidal agents, such as tartar emetic or bismuth phosphate. Single injections usually suffice. A suitable therapeutic dose of tartar emetic is a 5 c. c. of an M-10 (3·2 per cent.) solution per 100 lb. body weight. The treatment does not bring about a complete sterilization of the system of trypanosomes, which persist thereafter in the system in a latent state of activity, apparently indefinitely. The results obtained after treatment with tryparsamide do not appear to be appreciably superior.

B. Equines.

"*Bayer 205*".—(*i*) The results obtained by the application of "Bayer 205" surpass those obtainable by other medicaments.

(*ii*) A suitable therapeutic dose for intravenous administration is 5 grams, in 10 per cent. aqueous solution, per 1,000 lb. body weight.

(*iii*) The drug remains in the general circulation for a long time, apparently about two months, in sufficient concentration to exert a manifest trypanocidal action; hence, in species of such high susceptibility as the horse, which exhibits progressively increasing vulnerability with each parasitic relapse—in contradis-

tinction to what transpires with the bovine species, which is usually able to defend itself after assistance from a chemotherapeutic agent in the course of virulent invasion—the lack of liability to the rapid excretion characteristic of the other trypanocidal agents employed (presumably attributable to its large molecular structure) is a property of great importance, and fortifies the patient in withstanding relapses, from " tissue backwashes," until the risk of such relapses disappears.

(*iv*) The lack of diffusibility of the drug, however, operates adversely in one important respect, namely, in that it is unable to penetrate the subarachnoid space in trypanocidal concentration; hence, although prolonged sterilization of the circulatory system may be effected by the administration of a single intravenous dosage, in well-established cases of infection the trypanosomes meanwhile multiply, as has been proved by experimental observations, in the safe retreat afforded by the cerebro-spinal canal, and the animal may ultimately succumb from surra affecting purely the central nervous system. This defect may be counteracted by the introduction of " Bayer 205 ", simultaneously with the intravenous injection, intrathecally, in very dilute solution, in a dosage arithmetically equivalent to that introduced intravenously, having regard to the relative weights (about 1 : 500) of the tissues affected by the introduction of the drug into the two channels. The intrathecal dose thus applied has been 20 c. c. of a 0·1 per cent. solution per 1,000 lb. body weight injected, according to the methods described, through the occipito-atlantal space. Intravenous treatment alone, especially if repeated in full dosage after a month's interval, is sufficient to bring about prolonged sterilization in very early cases of infection; curiously, in some of these cases invasion of the cerebro-spinal axis had already occurred at the time of treatment.

(*v*) The therapeutic dose of " Bayer 205 " noted above may be safely introduced into the cirulating blood when large numbers of trypanosomes are present in it; complete disappearance takes place after a prolonged interval amounting to several hours, and thus the alarming symptoms set up by some other drugs due to rapid destruction of the parasites are not seen. Symptoms of drug intoxication, manifested notably in the form of locomotor disturbances closely simulating those of laminitis, and urticaria, may appear following upon the intravenous injection, but these symptoms disappear after a few days and are not to be feared. In some of our animals, the combined intravenous-intrathecal treatment has been repeated after a month's interval, in order to maintain the drug in trypanocidal concentration in the system for a longer period, to combat the possibility of relapse; this treatment has been quite successful, but the symptoms of drug intoxication appear to be more severe after the second injection, and the interference appears to be somewhat too drastic for horses in very low condition. The intrathecal injection has been repeated at shorter intervals (fortnightly) with perfect safety.

(*vi*) Our experiments would seem to show that " Bayer 205 " might be used with much advantage as a prophylactic agent, for the protection of horses exposed to surra in badly infected zones. Intravenous dosage, at the rate of about 1 gram

per 1,000 lb. body weight repeated fortnightly, would appear to suffice. However, experimental evidence has been adduced indicating that trypanosome infection, developing in horses during a stage after injection when the drug is present in insufficient concentration to arrest multiplication completely, is distinctly less amenable to the effects of the drug than infection in horses not previously treated; the difference in effect would appear to be due to the acquisition of a notable degree of " drug-fastness " by the trypanosomes exposed to the sublethal concentration of the drug. These observations would also lend further support to the view that in therapeutic treatment early intervention with the largest dosages capable of being supported by the infected animal is the method of treatment most likely ultimately to secure complete sterilization which again appears to be an essential condition for the establishment of a clinical cure in such highly susceptible species as the equine species.

(*vii*) There would appear to be no advantage in combining " Bayer 205 " with other trypanocidal agents in treatment, as has been advocated by other workers: at any rate, our results as they stand in their present stage of observation would indicate that, when suitably administered, prolonged sterilization can be obtained by means of " Bayer 205 " alone. Our knowledge regarding the ready multiplication of persisting trypanosomes in the tissues of the horse gives us further cause for belief that the sterilization has been complete as the observation periods in many instances have extended much beyond the estimated duration of persistence of " Bayer 205 " in the circulation.

(*viii*) *Tartar emetic.* This antimony compound comes next in value to, though far behind, " Bayer 205 ". The prophylactic effect, *vis-à-vis* a subsequent injection with virulent blood, is a short one, hardly exceeding 24 hours after intravenous inoculation with dosages of 5 c. c. of an M-10 (3·2 per cent.) solution per 100 lb. body weight, thus indicating that the drug is excreted relatively quickly. In therapeutic treatment, the drug displays intense trypanocidal properties, and the dosage mentioned above, which can be safely tolerated by a healthy animal, when administered intravenously into a horse showing trypanosomes in its peripheral circulation, brings about disastrous results: the patient may be killed even before the termination of the injection; on examination of the peripheral blood the trypanosomes are also observed to have vanished, and hence it is presumed that death has been occasioned by the occlusion of the blood capillaries with dead trypanosomes, or, possibly, by the liberation of their toxic properties. In undertaking treatment with tartar emetic, care has therefore to be taken in the initial administration of the drug, by cleansing the blood stream safely of massive parasitic infection, either (*a*) by commencing with very small doses of tartar emetic and gradually increasing the doses thereafter applied at frequent (daily or alternate day) intervals until the maximum safely tolerated dose of the healthy animal is reached, or (*b*) by a preliminary intravenous injection with a less drastic trypanocidal agent, such as tryparsamide or " Bayer 205 " (1 gram per 1,000 lb.), as has been adopted in experi-

ments recorded in this paper. On account of its liability to relatively rapid excretion the therapeutic dose must be repeated at frequent intervals, every day or every alternate day, as has been indicated by the experiments upon the prophylactic effect of the drug, until about ten or more such injections have been given. Apparently complete cure may be obtained by these means, as is illustrated by the records of one horse, in the early stage of infection and in good condition. Relapses may, however, subsequently arise, as is illustrated by the records of another horse, more severely affected at the time of treatment, and cerebro-spinal invasion may progress to a fata issue. Again, in animals in low condition, or possessing an idiosyncrasy towards the effects of the drug, death would appear to result from the drastic nature of the treatment.

(*ix*) *Bismuth compounds.* These compounds would appear to have much the same (though somewhat less intense and much less efficacious) action as the chemically related antimony preparations, studied in the form of tartar emetic. Their study was commenced as it was believed that an alternation of treatment with the simpler known trypanocidal agents would enable us to circumvent the problem of "drug-fastness," but the acquisition later of supplies of " Bayer 205 " and the indications of preliminary general experiments resolved us to devote our attention to the more concise channels of investigation that form the basis of the earlier conclusions.

(*x*) *Tryparsamide.* This organic arsenical compound, which would seem to hold the field now with " Bayer 205 " as the remedy that has given the most encouraging results in the treatment of human sleeping sickness, proved entirely disappointing in our hands. Workers with the human disease would appear to stress its remarkable property of diffusibility, which would render it capable of producing a distinct amelioration of the effects of infection within the cerebro-spinal canal and, probably, exercise a beneficial effect upon the glandular affection well known to workers with the human infection but unfamiliar to workers upon surra. The property of diffusibility measured in terms of rapid excretion were readily demonstrable in our experiments, as large dosages of the drug failed to exhibit any distinct prophylactic effect *vis-à-vis* a virulent infection even when administered simultaneously. From the therapeutic standpoint, the rapid excretion of the drug would again appear to explain the inability of the drug to produce sterilization for more than relatively short periods of time ; and, again, on repetition of the treatment, relapses occurred with increasing frequency, indicating that the trypanosomes developed readily a striking degree of " drug-fastness," towards the substance. A property of importance in connection with the drug, however, is that it exercises a slow and certain lethal action upon the trypanosomes in the circulating blood, analogous to that displayed by " Bayer 205 " in this respect, and hence it would seem that it might be employed with safety as a clearing agent prior to the application of repeated treatment with the more drastic trypanocidal agent, tartar emetic. The relatively high cost of the drug would also be a limiting factor in its application to the treatment of surra in horses. It is recognized that

in the human subject, in which the reaction to trypanosome invasion assumes in natural circumstances a form very different from the acute, septicæmic picture presented by infection in the equine subject, the properties peculiar to the drug such as tryparsamide may be of specific advantage. In some of our experiments, tryparsamide was used for the intrathecal injection of infected subjects.

(*xi*) *General.* "Bayer 205" gave by far the most satisfactory results of the drugs studied, when administered alone, intravenously and intrathecally, in suitable large initial doses, preferably repeated after a month's interval, in the course of treatment of cases of surra corresponding in gravity with those most likely to be encountered in the field. *See* Addendum slip. The drugs studied may be regarded as "types" illustrative of the best materials hitherto evolved for the chemotherapy of trypanosomiasis, differing among themselves on employment in certain important characteristics manifest to the clinician or pathologist. It is not unlikely that the chemist may be able in the near future to prepare substances possessing still more strikingly some of these, or even additional, characteristics. However, it would seem that those possessed by "Bayer 205" are in the direction of the most essential characteristics desired in a chemotherapeutic substance for the treatment of equine surra, namely, an assured toxicity, slow in effect for the parasite, relatively low toxicity at the therapeutic dose for the host, and long retention in trypanocidal concentration in the system—connoting low diffusibility, with consequent lack of power to traverse the meninges and affect cerebro-spinal infection, which last has to be overcome by direct intrathecal injection.

VII. Acknowledgments.

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Addendum to "Summary and Conclusions."

Routine Treatment of Equine Surra.

As the result of further experience, it may be stated more precisely that the routine treatment recommended for equine surra follows closely that found successful in the pony experiment described on page 25 of this *Memoir* :—

I. On diagnosis :—

(*a*) Inject 50 c. c. of a 10 per cent. solution of "Bayer 205" intravenously, per 1,000 lbs. body weight.

(If the horse is in very low condition, administer one-half this dose, and give the remaining half a week later, or as soon as the horse shows appreciable improvement in condition.)

(*b*) Inject 20 c. c. of a 0·1 per cent. solution of "Bayer 205" intrathecally, per 1,000 lbs. body weight.

(The solution for intrathecal injection is made by taking 1 c. c. of the solution for intravenous injection, and adding sterile water or normal saline solution to make up 100 c. c. of dilution.)

II. 15 days after *I*. Repeat *I* (*b*), only.

III. 15 days after *II*. Repeat *I* (*a*) (*i.e.*, full intravenous dose), and *I* (*b*).

No further medical treatment required: attend carefully to restoration in bodily condition, by good feeding and graded exercise.

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IX. Tables.

Table I.

Details of inoculation of virus into 22 horses.

Serial No.	Animal	Source of virus	Trypanosomes	Date of inoculation	Period of incubation	Interval between inoculation and death or treatment	Remarks
1	Horse 65	Rabbit 270	25 per field	Sept. 22	90 hours	7 days (D)	Centrifuged Cerebrospinal fluid showed trypanosomes 2 per field.
2	Mare 2	,, 143*a**	Swarming	July 15	89 ,,	21 ,, (T)	
3	Horse 53	,, 272*.	20 per field	Aug. 2	5 days	25 ,, (T)	
4	,, 54	,, 147*a**	10 ,, ,,	,, 11	4 ,,	20 ,, (T)	
5	,, 19	,, 143*a**	Swarming	July 15	4 ,,	21 ,, (T).	
6	,, 3	,, 143*a**	,,	,, 15	4 ,,	21 ,, (T).	
7	,, 47	,, 148*a*.	Few	,, 23	5 ,,	24 ,, (T).	
8	,, 69	,, 230*a**	6 per field	Sept. 4	5 ,,	20 ,, (T).	
9	Donkey 35	,, 250*a*.	Few	Oct. 14	4 ,,	7 ,, (T).	
10	,, 41	,, 284*a**	8 per field	,, 8	4 ,,	5 ,, (T).	
11	,, 36	,, 184*a**	Not recorded	,, 6	5 ,,	8 ,, (T).	
12	Pony 85	G. pig 202*a*	12 per field	Nov. 27	5 ,,	8 ,, (T).	
13	,, 74	,, 202*a*	Ditto	,, 27	5 ,,	8 ,, (T).	
14	,, 76	,, 202*a*	Ditto	,, 27	5 ,,	8 ,, (T).	
15	,, 80	,, 202*a*	Ditto	,, 27	5 ,,	8 ,, (T).	
16	,, 77	,, 202*a*	Ditto	,, 27	5 ,,	8 ,, (T).	
17	,, 79	,, 202*a*	Ditto	,, 27	6 ,,	8 ,, (T).	
18	,, 78	,, 202*a*	Ditto	,, 27	5 ,,	8 ,, (T).	
19	,, 86	,, 202*a*	Ditto	,, 27	4 ,,	8 ,, (T).	
20	,, 84	,, 202*a*	Ditto	,, 27	5 ,,	8 ,, (T).	
21	,, 83	,, 202*a*	Ditto	,, 27	6 ,,	7 ,, (D).	Control animal.
22	,, 82	,, 202*a*	Ditto	,, 27	5 ,,	9 ,, (D).	Control animal.

N.B. The strain employed was the "Peora" strain, except those marked with an asterisk. With the exception of the first eight animals, all were injected with virulent blood by the intrathecal route.

T. Treated.
D. Died.

Table II.

Showing the results of intrathecal injection of varying doses of "Bayer 205."

Animal	Body weight lb.	Concentration used	Total quantity of solution injected	Calculated approximate rate per 1,000 lb. Grm.	Death
Foal 56	200	10 per cent.	1	0·5	†95 mins. (Chloroformed to death. See text.)
,, 49	154	1 ,,	3·1	0·2	—
,, 72	236	2 ,,	1·18	0·2	—

TABLE III.

Result of blood examination after single doses of "Bayer 205."

Animal	Dose of "Bayer 205" grm. per 1,000 lb.		Result of Examination of Blood for Trypanosomes after Treatment																														Time of negative examination after treatment	Remarks
	Intravenous	Intrathecal	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	7 hrs.	8 hrs.	9 hrs.	10 hrs.	11 hrs.	12 hrs.	13 hrs.	14 hrs.	15 hrs.	16 hrs.	17 hrs.	18 hrs.	19 hrs.	20 hrs.	21 hrs.	22 hrs.	23 hrs.	24 hrs.	25 hrs.	26 hrs.	27 hrs.	28 hrs.	29 hrs.	30 hrs.	31 hrs.	32 hrs.	33 hrs.	34 hrs.		
																																			Hours.	
Mare 2	5	..			+																			+										24	
,, 2	1	0·01																																	40*	Relapsed case.
Horse 53	1	..		+			+			+													+												25	
,, 53	1	..		+			+			+									+		+			+											28*	Relapsed case.
,, 54	0·5	..																																	24	
,, 19	1	..			+																														24	
,, 64	5	..		+			+						—											—												12	Also confirmed by sub-inoculation of blood into guinea-pigs.
,, 67	5	..																																	24	
,, 46	5	0·02																																	24	Treated prophylactically with "Bayer 205."
Donkey 35	5	0·02																																	24	
Mare 57	5	0·02																																	24	Treated prophylactically with "Bayer 205."
Pony 85	5	0·02																																	24	
,, 74	2·5	..																																	24	
,, 76	2·5	..																																	24	
,, 80	5	..																																	24	
,, 77	2·5	0·02																																	24	
,, 79	5	..																																	24	
,, 78	2·5	0·02																																	24	
,, 86	2·5	0·02																																	24	
,, 84	5	0·02																																	24	
Horse 70	5	0·02																																	24	
,, 45	5	0·02																																	24	
,, 59	1	..	+	+	+	+	+		+																		+		+						30	
,, 59	1	..		+			+														+			+		+				+				40	Relapsed case.

TABLE IV.

Summary of relapses and non-relapses.

No.	Animal.	Time of drug intervention after infective inoculation	Dose of "Bayer 205" in grams per 1,000 lb. body weight		Result	Remarks
			Intravenous	Intrathecal		
					Days	
1	Mare 2	21 days	5	..	+47	Retreated [see Table 5].
2	Horse 53	25 ,,	1	..	+11	Ditto [see Table 9].
3	,, 19	21 ,,	1	..	+23	Ditto [see Table 5].
4	,, 3	21 ,,	2·5	..	—30	Died. Centrifuged cerebrospinal fluid swarming with trypanosomes.
5	,, 26†	33 ,,	5	0·02	—404	Discontinued.
6	,, 35	18 ,,	5	0·02	—419	Discontinued.
7	Mare 68	19 ,,	5	0·02*	+21	Retreated [see Table 5].
8	Horse 64	20 ,,	5	..	—30	Ditto
9	,, 67	5 ,,	5	..	—392	Discontinued.
10	,, 46†	39 ,,	5	0·02	—398	Discontinued.
11	,, 69	19 ,,	5	0·02	—30	Retreated [see Table 5].
12	,, 21A	24 ,,	5	0·02	—30	Ditto
13	Donkey 35	7 ,,	5	0·02	—421	Discontinued.
14	,, 4	1 day	5	0·02	—421	Discontinued.
15	,, 13	1 ,,	5	..	—152	Died of debility.
16	,, 41	5 days	5	..	—429	Discontinued.
17	,, 36	7 ,,	5	0·02	—429	Discontinued.
18	,, 11	1 day	5	0·02	—421	Discontinued.
19	,, 17	1 ,,	5	0·02	—421	Discontinued.
20	Mare 57†	21 days	5	0·02	+45	Retreated [see Table 5].
21	Horse 28†	52 ,,	5	0·02	+21	Ditto
22	,, 63†	10 ,,	5‡	0·02	+138	Died.
23	Pony 85	8 ,,	5	0·02	—16	Retreated [see Table 5].
24	,, 74	8 ,,	2·5	..	—30	Ditto
25	,, 76	8 ,,	2·5	..	—30	Ditto
26	,, 80	8 ,,	5	..	—30	Ditto
27	,, 77	8 ,,	2·5	0·02	—16	Ditto
28	,, 79	8 ,,	5	..	—30	Ditto
29	,, 78	8 ,,	2·5	0·02	—16	Ditto
30	,, 86	8 ,,	2·5	0·02	—16	Ditto
31	,, 84	8 ,,	5	0·02	—16	Ditto
32	Horse 45	33 ,,	5	0·02	—6	Died. Trypanosomes present in centrifuged cerebrospinal fluid.
33	,, 70	19 ,,	5	0·02*	—30	Retreated [see Table 5].
34	,, 59	20 ,,	1	..	+8	Ditto

* Used Tryparsamide.
† Treated prophylactically with "Bayer 205."
‡ A portion of drug escaped due to struggling [see protocol].

TABLE V.

Treatment with repeated doses of "Bayer 205."

Animal	Date of infective inoculation	Dose in grams per 1,000 lb. body weight		Result	Remarks
		Intravenous	Intrathecal		
				Days	
Mare 2†	July 15th	5·0 Aug. 5th 1·0 Sept. 21st	0·010 Sept. 21st	D. 2.	
Horse 59†	Aug. 2nd	1·0 Aug. 22nd 1·0 Sept. 2nd 1·0 Sept. 11th	0·2 Sept. 20th	D. 1.	
Horse 19	July 15th	1·0 Aug. 5th 5·0 Aug. 28th	..	D. 1.	
Mare 68†	Sept. 4th	5·0 Sept. 23rd 5·0 Oct. 23rd	0·02* Sept. 23rd 0·02* Oct. 23rd	N.R. 419	Discontinued.
Horse 64	Sept. 9th	5·0 Sept. 24th 5·0 Oct. 23rd	..	N.-R. 419	Discontinued.
„ 69	Sept. 4th	5·0 Sept. 23rd 5·0 Oct. 23rd	0·02 Sept. 23rd 0·02 Oct. 23rd	N.-R. 419	Discontinued.
„ 21A	Aug. 29th	5·0 Sept. 23rd 5·0 Oct. 23rd	0·02 Sept. 23rd 0·02 Oct. 23rd	N.-R. 419	Discontinued.
„ 57†	Oct. 5th	5·0 Oct. 26th 5·0 Dec. 21st	0·02 Oct. 26th 0·02 Dec. 21st	N.-R. 42.	Died of suspected schistosomiasis.
„ 28†	Sept. 22nd	5·0 Nov. 13th 5·0 Dec. 21st	0·02 Nov. 13th 0·02 Dec. 21st	N.-R. 360	Discontinued.
Infected intrathecally—					
Pony 85	Nov. 27th	5·0 Dec. 5th 5·0 Jan. 4th	0·02 Dec. 15th 0·02 Dec. 21st 0·02 Jan. 4th	N.-R. 7.	Died of pleuro-pneumonia.
„ 74	Nov. 27th	2·5 Dec. 5th 2·5 Jan. 4th	..	R. 71.	Died.
„ 76	Nov. 27th	2·5 Dec. 5th 2·5 Jan. 4th	..	R. 41.	Died.
„ 80	Nov. 27th	5·0 Dec. 5th 5·0 Jan. 4th	..	N.-R. 346.	
„ 77	Nov. 27th	2·5 Dec. 5th 2·5 Jan. 4th	0·02 Dec. 5th 0·02 Dec. 21st 0·02 Jan. 4th	N.-R. 346.	

* Used Tryparsamide.
† Represents relapsed case.
D. Died.
R. Relapsed.
N.-R. Did not relapse.
The results recorded above are for observation periods extending to 16th December 1926.

TABLE V—*concld.*

Treatment with repeated doses of "Bayer 205"—contd.

Animal	Date of infective inoculation	Dose in grams per 1,000 lb. body weight		Result	Remarks
		Intravenous	Intrathecal		
				Days	
Infected intrathecally—					
Pony 79	Nov. 27th	5·0 Dec. 5th 5·0 Jan. 4th	..	N.-R. 346.	
„ 78	Nov. 27th	2·5 Dec. 5th 2·5 Jan. 4th	0·02 Dec. 5th 0·02 Dec. 21st 0·02 Jan. 4th	N.-R. 346.	
„ 86	Nov. 27th	2·5 Dec. 5th 2·5 Jan. 4th	0·02 Dec. 5th 0·02 Dec. 21st 0·02 Jan. 4th	N.-R. 346.	
„ 84	Nov. 27th	5·0 Dec. 5th 5·0 Jan. 4th	0·02 Dec. 5th 0·02 Dec. 21st 0·02 Jan. 4th	N.-R. 346.	
Horse 70	Sept. 4th	5·0 Sept. 23rd 5·0 Oct. 23rd	0·02* Sept. 23rd 0·02* Oct. 23rd	N.-R. 10.	Died. Cause of death undetermined.

* Used Tryparsamide.
N.-R. Did not relapse.
The results recorded above are for observation periods extending to 16th December 1926.

TABLE VI.

Summary of results of prophylactic treatment with "Bayer 205."

Animal	Dose in grams per 1,000 lb. body weight		Interval between treatment and infective inoculation	Result	Incubation period
	Intravenous	Intrathecal			
Horse 2c	7·5 July 20th	..	22 days	—	.
„ 26	7·5 July 20th	..	77 „	+	6 days
„ 46	5·0 July 23rd	..	*Nil*	—	..
„ 46	5·0 July 23rd	..	74 days	+	4 days.
Mare 57	1·0 Aug. 2nd	..	*Nil*	—	..
„ 57	1·0 Aug. 2nd	..	64 days	+	6 days.
Horse 28	10·0 July 20th	..	64 „	+	6 „
„ 63	..	0·02 Sept. 22nd 0·02 Oct. 7th	38 „	+	4 „
„ 21B	5·0 July 20th	..	3 „	—	..
„ 21B	5·0 July 20th	..	77 „	+	6 days.

TABLE VII.

Lethal effects obtained with M/10 tartar emetic in cattle.

Rate of solution per kilo body weight	Result
1 c.c. (1)	Succumbed.
0·6 c.c. (1)	
0·5 c.c. (4)	
0·4 c.c. (4)	
0·35 c.c. (2)	
0·3 c.c. (3)	Only one succumbed.

N.B. The numbers in brackets represent the number of animals tested.

TABLE VIII.

Effect of tartar emetic on buffaloes artificially infected with surra. M/10 solution of tartar emetic used.

Animal	Date of infective inoculation	Date of treatment with drug	Dose per 100 lb. b.-w.	Dates of positive examination of blood*	Result	REMARKS
			c.c.			
Buffalo 108	Nov. 8th	Nov. 17th	5	Nov. 14th-18th Nov. 27th-29th	Died Nov. 29th.	
,, 114	Nov. 8th	Nov. 17th	5	Nov. 14th-17th Nov. 28th Mar. 23rd	Alive Mar. 24th.	
,, 171	Jan. 17th	Jan. 22nd	5	Jan. 21st-22nd	Died Jan. 25th.	
,, 175	Jan. 17th	Jan. 22nd	5	Jan. 21st-22nd Feb. 1st-4th Feb. 7th-10th.	Died Feb. 10th.	
,, 169	Jan. 17th	Jan. 22nd	5	Jan. 21st-22nd	Died Jan. 27th.	
,, 172	Jan. 17th	Jan. 22nd	2·5	Jan. 21st—Mar. 20th [re-appearances at irregular intervals.]	Alive Mar. 24th.	
,, 180	Jan. 17th	Jan. 22nd	2·5	Jan. 21; Jan. 30th—Feb. 3rd; Feb. 6th.	Died Feb. 6th.	
,, 151	Jan. 17th	Jan. 22nd	1·25	Jan. 21st—22nd; Jan. 29th—Mar. 7th [intermittent re-appearances].	Died Mar. 7th.	
,, 179	Jan. 17th	Jan. 22nd	1·25	Jan. 21st-22nd; Jan. 29th—Feb. 14th [intermittent re-appearances].	Died Feb. 14th.	
,, 183	Feb. 18th	Mar. 7th	5	Mar. 7th	Died Mar. 8th.	Weak at time of inoculation.
,, 207	Feb. 18th	Mar. 7th	5	Feb. 27th-28th Mar. 6th-7th Mar. 26th-27th	Alive Mar. 28th.	
,, 304	Feb. 18th	Mar. 7th	5	Mar. 1st; Mar. 7th Mar. 19th-20th.	Alive Mar. 28th.	

TABLE VIII—*concld.*

Effect of tartar emetic on buffaloes artificially infected with surra. M/10 solution of tartar emetic used. —contd.

Animal	Date of infective inoculation	Date of treatment with drug	Dose per 100 lb. b.-w.	Dates of positive examination of blood*	Result	REMARKS
			c.c.			
Buffalo 173 .	Feb. 18th .	Mar. 7th .	2·5	Feb. 28th-29th . .	Alive Mar. 28th.	
				Mar. 7th . . .		
				Mar. 19th-24th . .		
,, 97 .	Feb. 18th .	Mar. 7th .	2·5	Mar. 7th . . .	Alive Mar. 28th.	
				Mar. 17th-28th . . [intermittent re-appearances].		
,, 109 .	Feb. 18th .	Mar. 7th .	2·5	Mar. 3rd . .	Alive Mar. 28th.	
				Mar. 6th . .		
,, 665 .	Feb. 18th .	Mar. 7th .	1·25	Feb. 25th-26th; Mar. 7th; Mar. 14th-28th [intermittent re-appearances].	Alive Mar. 28th.	
,, 92 .	Feb. 18th .	Mar. 4th	1·25	Feb. 25th—Mar. 7th .	Alive Mar. 28th.	
,, 261 .	Feb. 18th .	Mar. 7th .	1·25	Feb. 22nd—Mar. 7th [intermittent re-appearances]; Mar. 15th-28th [intermittent re-appearances].	Alive Mar. 28th.	

* Results of examination of blood smears on dates other than those mentioned in this column were negative for trypanosomes.

TABLE IX.

Results of treatment by means of tartar emetic combined with "Bayer 205" or tryparsamide. M/10 solution of tartar emetic used.

Animal	Date of infective inoculation	Treatment	Result	REMARKS
			Days.	
Horse 53 . . .	Aug. 2nd .	1·0 B August 27th, September 8th; 5·0 E September 11th, 14th, 17th, 20th, 23rd.	D. 2 . .	Trypanosomes seen in cerebrospinal fluid.
,, 54 . . .	Aug. 11th .	0·5 B August 29th; 5·0 E August 31st, September 2nd, 4th.*	Destroyed 17	Developed paraplegia. Centrifuged cerebrospinal fluid showed trypanosomes 8 per field.
,, 51 . . .	Aug. 11th .	9·0 T August 11th, 22nd, 30th, September 15th; 5·0 E September 1st, 3rd, 5th, 17th, 19th, 21st, 23rd, 25th, 27th, 29th, October 1st, 3rd, 5th.	N.-R. 487 .	Discontinued.
,, 48 . . .	Aug. 11th .	9·0 T August 31st; 5·0 E September 3rd, 6th, 9th, 12th, 15th, 18th, 21st, 24th, 27th, 30th.	R. 13 .	Died. Trypanosomes in cerebrospinal fluid.

* Treated with "Bayer 205" on day previous to death at 1 gram intravenously and 0·02 gram intrathecally per 1,000 lb.

B="Bayer 205."
T=Tryparsamide.
E=Tartar emetic.
D=Died.
R=Relapsed.
N.-R=Did not relapse.

The dosage is in grams per 1,000 lb. body weight for "Bayer 205" and Tryparsamide, and in c.c. per 100 lb. body weight for tartar emetic.

TABLE X.

Summary of results of prophylactic treatment with tartar emetic. M/10 solution of tartar emetic used.

Animal	Dose in c.c. per 100 lb. body weights	Interval between treatment and infective inoculation	Result	Incubation period
Horse 23	5·0 daily July 18th—August 3rd*.	8 days	+	6 days.
„ 35	10·0 daily July 19th-22nd	1 day	—	..
„ 35	10·0 daily July 19th-22nd	75 days	+	5 days.
„ 68	5·0 daily August 28th-30th	5 „	+	6 „
„ 64	5·0 daily September 1st-3rd	1 day	+	6 „
„ 21A	2·0 daily July 17th—August 3rd	26 days	+	6 „
„ 45	10·0 July 23rd	*Nil*	—	..
„ 45	10·0 July 23rd	74 days	+	5 days.
„ 70	5·0 daily August 30th—September 1st.	3 „	+	5 „

* The whole quantity could not be injected on August 3rd as horse became refractory.
+ indicates that infection occurred.
— indicates that infection did not occur.

TABLE XI.

Effect of tryparsamide on buffaloes artificially infected with surra.

Animal	Date of infective inoculation	Date of treatment with drug	Dose per kilo body weight	Dates of positive examination of blood*	Resut	REMARKS
			grm.			
Buffalo 184	Jan. 17th.	Jan. 22nd	0·5	Jan. 21st-22nd	Died Jan. 26th.	
„ 181	Jan. 17th.	Jan. 22nd	0·5	Ditto	Died Jan. 22nd.	
„ 186	Jan. 17th.	Jan. 22nd	0·5	Ditto	Died Jan. 26th.	
„ 174	Jan. 17th.	Jan. 22nd	0·25	Ditto	Ditto.	
„ 182	Jan. 17th.	Jan. 22nd	0·25	Ditto	Died Jan. 27th.	
„ 176	Jan 17th.	Jan 22nd	0·25	Ditto	Died Jan. 22nd.	
„ 153	Jan. 17th.	Jan. 22nd	0·125	Jan. 21st-22nd Feb. 1st-3rd Feb. 10th-11th	Died Feb. 11th.	
„ 177	Jan. 17th.	Jan. 22nd	0·125	Jan. 21st-24th	Died Jan. 28th.	
„ 661	Feb. 18th.	Feb. 27th.	0·2	Feb. 27th	Alive Mar. 28th.	
„ 663	Feb. 18th.	Feb. 27th.	0·2	Feb. 22nd-27th [irregular re-appearances].	Died Mar. 5th.	

TABLE XI—*concld.*

Effect of Tryparsamide on buffaloes artificially infected with surra—contd.

Animal	Date of infective inoculation	Date of treatment with drug	Dose per kilo body weight	Dates of positive examination of blood*	Result	REMARKS
Buffalo 669 .	Feb. 18th .	Feb. 27th .	0·2	Feb. 25th-27th . .	Died Mar. 8th.	
,, 670 .	Feb. 18th .	Feb. 27th .	0·1	Feb. 22nd-27th [irregular reappearances].	Died Mar. 12th.	
,, 672 .	Feb. 18th .	Feb. 27th .	0·1	Feb. 22nd-27th . .	Alive Mar. 28th.	
,, 662 .	Feb. 18th .	Feb. 27th .	0·1	Feb. 22nd-27th . .	Ditto.	
				Mar. 15th-16th . .		
,, 314 .	Feb. 18th	Feb. 29th .	0·05	Feb. 28th-29th . .	Ditto.	
		Mar. 21st .	0·05	Mar. 15th-16th .		
,, 102 .	Feb. 18th	Feb. 29th .	0·05	Feb. 21st-22nd . .	Ditto.	
		Mar. 21st .	0·05			
,, 218 .	Feb. 18th *	Feb. 29th	0·05	...	Ditto.	No trypanosomes were discoverable.
		Mar. 21st .	0·05			

* Results of examination of blood smears on dates other than those mentioned in this column were negative for trypanosomes.

TABLE XII.

Lethal effects obtained with tryparsamide in cattle.

Rate per kilo in grams	Result
0·75 (1)	Succumbed.
0·5 (5)	
0·4 (1)	
0·25 (2)	
0·2 (4)	Only one (buffalo) survived.

N.B. The figures in brackets represent the number of animals tested. The animals included 4 hill bulls and 9 buffaloes. Of the 4 animals which received the drug at the rate of 0·2 gram per pilo, one only was a hill bull.

TABLE XIII.

Summary of results of prophylactic treatment with tryparsamide

Animal	DOSE IN GRAMS PER 1,000 LB.		Interval between treatment and infective inoculation	Result	Incubation period
	Intravenous	Intrathecal			
Mare 67	..	0·02 Sept. 22nd 0·02 Oct. 7th	38 days .	+	5 days.
Horse 51	9·0 Aug. 11th	..	*Nil* . . .	+	5 ,,

TABLE XIV.

Lethal effects obtained from the administration of a suspension of bismuth phosphate in glucose solution to horses, intravenously.

Animal	Strength of drug	Dose in c. c. per 100 lb.	Intoxication	Death	REMARKS
Horse 55 .	25%	17	+	+½ hour	Drug administered in two doses of equal size at an interval of ½ hour; no symptoms after the first injection.
,, 1 .	25%	10	+	+¼ hour	

TABLE XV.

Lethal effects obtained from the administration of a bismuth sodium tartrate solution to horses, intravenously.

Animal	Strength of drug	Dose in c. c. per 100 lb.	Intoxication	Death	REMARKS
	Per cent.				
Horse 62 . . .	4	2	+	+½ hr.	2 doses given with interval of 24 hrs.
,, 50 . . .	8	1·35	+	+½ hr.	

TABLE XVI.

Summary of results of prophylactic treatment with bismuth compounds.

[4 per cent. solution of bismuth sodium tartrate and 25 per cent. suspension of bismuth phosphate in glucose solution used.]

Animal	DOSE IN C.C. PER 100 LB. BODY WEIGHT		Interval between treatment and infective inoculation	Result	Incubation period
	Bismuth sodium tartrate	Bismuth phosphate			
Horse 61	1·0 daily Aug. 19th-28th.	..	1 day . .	+	5 days.
,, 59	..	5·0 daily July 30th-Aug. 1st.	1 ,, .	+	5 ,,
,, 58	..	5·0 Aug. 8th .	*Nil* . .	+	5 ,,
,, 48	..	2·5 daily Aug. 1st-10th.	1 day . .	+	6 ,,

+ Denotes that infection occurred.

TABLE XVII.

Statement of Sub-inoculations.

No.	From	Into	Date of sub-inoculation	Material sub-inoculated	Result	Incubation period	REMARKS
1	Horse 26 .	Dog 38 .	4 P.M., 29th Aug. 1925	Citrated blood	—	..	Discontinued 22nd Sept. 1925.
2	,, 35 .	,, 31 .	Ditto .	Ditto .	—	..	D. 7th Sept. 1925.
3	,, 59 .	G. pig 169 .	4-40 P.M., 20th Sept. 1925.	Cerebrospinal fluid	+	27 days .	D. 18th Dec. 1925.
4	,, 59 .	,, 168 .	Ditto .	Ditto .	+	24 ,,	D. 26th Nov. 1925.
5	,, 3 .	,, 154 .	4th Sept. 1925 .	Citrated blood	—	..	Discontinued 23rd Sept. 1925.
6	,, 3 .	,, 155 .	Ditto .	Ditto .	—	..	Ditto.
7	,, 3 .	,, 153 .	Ditto .	Ditto .	—	..	Ditto.
8	,, 64 .	,, 164[1] .	9 A.M., 24th Sept. 1925.	Ditto .	+	7 days .	D. 14th Oct. 1925.
9	Ditto .	,, 173[1] .	Ditto .	Ditto .	+	10 ,, .	D. 17th Nov. 1925.
10	Ditto .	,, 166[2] .	12 noon, 24th Sept. 1925.	Ditto .	+	26 ,, .	D. 1st Dec. 1925.
11	Ditto .	,, 167[3] .	Ditto .	Ditto .	—	..	Discontinued 23rd Mar. 1926.
12	Ditto .	,, 170[3] .	3 P.M., 24th Sept. 1925.	Ditto .	+	23 days .	D. 18th Nov. 1925.
13	Ditto .	,, 171[3] .	Ditto .	Ditto .	+	31 ,,	Recovered. Discontinued 23rd Mar. 1926.
14	Ditto .	,, 165[4] .	9 P.M., 24th Sept. 1925.	Ditto .	—	..	Discontinued 23rd Mar. 1926.
15	Ditto .	,, 172[4] .	Ditto .	Ditto .	—	..	Ditto
16	Ditto .	,, 174[5] .	9 A.M., 25th Sept. 1925.	Ditto .	—	..	Ditto.
17	Ditto .	,, 175[5] .	Ditto .	Ditto .	—	..	Ditto.
18	Horse 51 .	,, 194 .	4-30 P.M., 6th Oct. 1925.	Cerebrospinal fluid.	—	..	D. 8th Oct. 1925.
19	Ditto .	,, 195 .	Ditto .	Ditto .	—	..	D. 25th Oct. 1925.
20	Ditto .	Rabbit 354 .	4-30 P.M., 6th Oct. 1925.	Ditto	—	..	D. 16th Nov. 1925.
21	Horse 48 .	G. pig 197 .	Ditto .	Ditto .	+	26 days .	D. 23rd Nov. 1925.

[1] = Sub-inoculated before treatment of horse with "Bayer 205."
[2] = Sub-inoculated 3 hours after treatment of horse with "Bayer 205."
[3] = Sub-inoculated 6 hours after treatment of horse with "Bayer 205."
[4] = Sub-inoculated 12 hours after treatment of horse with "Bayer 205."
[5] = Sub-inoculated 24 hours after treatment of horse with "Bayer 205."
D = Died.

TABLE XVII—*concld.*

Statement of Sub-inoculations—contd.

No.	From	Into	Date of sub-inoculation	Material sub-inoculated	Result	Incubation period	REMARKS
22	Horse 48 .	G. pig 196 .	4-30 P.M., 6th Oct. 1925.	Cerebrospinal fluid.	+	26 days .	D. 3rd Dec. 1925.
23	Ditto .	Rabbit 355 .	Ditto .	Ditto .	+	17 „ .	D. 30th Oct. 1925.
24	Horse 67	„ 584 .	13thFeb.1926 .	Citrated blood	—	..	D. 16th Feb. 1926.
25	„ 67 .	„ 585 .	Ditto .	Ditto .	—	..	D. 11th Mar. 1926.
26	„ 46 .	„ 586 .	Ditto .	Ditto .	—	..	D. 26th Mar. 1926.
27	„ 46 .	„ 587 .	Ditto .	Ditto .	—	..	Discontinued 6thMay1926.
28	„ 69 .	„ 588 .	Ditto .	Ditto .	—	..	D. 18th Mar. 1926.
29	„ 69 .	„ 589	Ditto .	Ditto .	—	..	D. 27th Feb. 1926.
30	„ 64 .	„ 590 .	Ditto .	Ditto .	—	..	D. 8th Mar. 1926.
31	„ 64 .	„ 591 .	Ditto .	Ditto .	—	..	D. 16th Feb. 1926.
32	„ 26 .	„ 592 .	Ditto .	Ditto .	—	..	D. 27th Feb. 1926.
33	„ 26 .	„ 593	Ditto .	Ditto .	—	..	Discontinued 6th May1926.
34	„ 21 .	„ 594 .	Ditto	Ditto .	—	..	D. 20th Feb. 1926.
35	„ 21 .	„ 595 .	Ditto .	Ditto .	—	..	D. 15th Mar. 1926.
36	„ 63 .	„ 596 .	Ditto .	Ditto .	—	..	Discontinued 6thMay 1926.
37	„ 63 .	„ 597 .	Ditto .	Ditto .	—	..	D. 6th Mar. 1926.
38	„ 28 .	„ 598 .	Ditto .	Ditto .	—	..	Discontinued 6thMay1926.
39	„ 28 .	„ 599 .	Ditto .	Ditto .	—	..	D. 21st Feb. 1926.
40	„ 51 .	„ 600 .	Ditto .	Ditto .	—	..	D. 16th Feb. 1926.
41	„ 51 .	„ 601 .	Ditto .	Ditto .	—	..	D. 10th Mar. 1926.
42	„ 68 .	„ 602 .	Ditto .	Ditto .	—	..	D. 5th Mar. 1926.
43	„ 68 .	„ 603 .	Ditto .	Ditto .	—	..	Discontinued 6thMay1926.
44	„ 35 .	„ 604 .	Ditto .	Ditto	—	..	D. 28th Feb. 1926.
45	„ 35 .	„ 605 .	Ditto .	Ditto .	—	..	Discontinued 6th May 1926.
46	„ 51 .	Mule 1 .	5th Dec. 1925 .	Cerebrospinal fluid.	—	..	Discontinued 19th May 1926.
47	„ 57 .	Rabbit 579 .	1st Feb. 1926 .	Cerebrospinal fluid.	—	..	Discontinued 23rd Mar. 1926.
48	„ 57 .	„ 580 .	Ditto .	Citrated blood .	—	..	Discontinued 23rd Mar. 1926.
49	„ 57 .	G. pig 182 .	Ditto .	Ditto . .	—	..	Ditto.
50	„ 57 .	„ 103 .	Ditto .	Cerebrospinal fluid.	—	..	D. 24th Feb. 1926.
51	Pony 85 .	„ 184 .	9·55 A.M., 11th Jan. 1926.	Citrated blood	—	..	Discontinued 23rd Mar. 1926.

X. Protocols.

These protocols furnish brief histories, with charts indicating the daily temperatures and trypanosome "curves," of some of the equines employed in the experiments alluded to in the text of the paper. They were drafted at the Muktesar laboratory from the original animal charts prior to the author's departure on leave out of India at the end of February 1926. They have been emended in the galley proofs to incorporate the subsequent histories of surviving animals until the date (16th December 1926) on which the experiments were brought to a close. The individual histories of the bovines submitted to experiment are not included, as such would make the paper unwieldy and they are of relatively small importance so far as the main contentions formulated in this paper are concerned.

Action of tryparsamide, smaller doses, repeated frequently, upon naturally contracted surra in horse.

Pony 174. (Plate I.)

Maintained at Bareilly Branch Laboratory at same time as "Ekka" pony mare (*c.v.*).

25th September 1922. Injected 3 grams intravenously in 10 per cent. aqueous solution.

28th September 1922. Repeated treatment.

1st October 1922. Ditto.

4th October 1922. Ditto.

6th October 1922. Died.

(The above dosage of tryparsamide failed to sterilize peripheral circulation even temporarily.)

Therapeutic action of tryparsamide, in weekly doses of 10 grams administered intravenously, upon naturally contracted case of surra.

Ekka Pony Mare. (Plate I.)

25th September 1922. Injected 10 grams tryparsamide intravenously in 10 per cent. aqueous solution. Repeated above treatment weekly until 30th October 1922 (6 injections). Relapsed during, and just before termination of treatment.

10th November 1922. Injected 20 grams tryparsamide intravenously in 10 per cent. aqueous solution.

16th November 1922. Died.

Bismuth phosphate: estimation of toxicity.

Horse No. 1. 888 lb.

30th July 1925. 1-0 p.m. Injected, intravenously 45 c.c. of bismuth phosphate emulsion (1-4) (*see* text).

3·0 p.m. Injected again intravenously 45 c.c. of bismuth phosphate emulsion. About 4 minutes after the injection, began to show symptoms of dyspnœa, staggering gait, threw itself down violently, staggered convulsively, passed flatus, showed spasms of muscles, especially of neck, and died in this condition in about 10 minutes; passed urine at time of death.

Bismuth phosphate: estimation of toxicity.

Horse No. 55. 986 lb.

29th July 1925. Bismuth phosphate emulsion, 190 c.c. (at the rate of 20 c.c. per 100 lb. body weight) was to be injected intravenously. When about three-quarters of the emulsion had passed into the vein, the animal began to show signs of dyspnœa; by the time 170 c.c. had passed, the dyspnœa was distinct, and further injection was stopped. In a few minutes the horse became very much distressed, then fell down in a convulsion, with spastic contractions of muscles of neck. Pulse could not be taken owing to struggles of animal. Expired in about half an hour after onset of symptoms.

Bismuth sodium tartrate: estimation of toxicity.

Horse No. 62. 908 lb.

19th August 1925. 12·40 p.m. Injected intravenously 18 c.c. of a 4 per cent. solution of bismuth sodium tartrate, at the rate of 2 c.c. per 100 lb. body weight.

20th August 1925. 2·0 p.m. Repeated the above injection. Within a few minutes of the injection, fell down in a convulsion, and after a few more minutes showed spasmodic movements of legs and body, and then died at 2-30.

Bismuth sodium tartrate: estimation of toxicity.

Horse No. 50. 848 lb.

11th August 1925. 11 a.m. Injected intravenously 11·5 c.c. of 8 per cent. bismuth sodium tartrate solution, at the rate of 1·35 per 100 lb. body weight. A few minutes after the injection the horse began to show convulsive movements, fell down twice and got up within a few minutes; finally fell down and died within 5 minutes, showing spasms of muscles of neck and jaws and spasmodic movements of eyeballs.

(i) Tolerance to bismuth sodium tartrate (10 daily injections at 1 c.c. of a 4 per cent. solution per 100 lb. body weight); (ii) Prophylactic effect of same towards subcutaneous infection one day later, nil.

Horse No. 61. (Plate II.)

19th August 1925. 856 lb. 10 a.m. Injected intravenously 8·5 c.c. of a 4 per cent. solution of bismuth sodium tartrate, at the rate of 1 c.c. per 100 lb. body weight.
20-28th August 1925. Repeated daily the above injection.
29th August 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 235A, showing trypanosomes 1 in 2 fields.
8th September 1925. 822 lb.
13th September 1925. 820 lb.
14th September 1925 Weak, developed œdema of hind legs, conjunctival mucous membrane icteric.
16th September 1925. Weak; œdema hind legs.
17th-22nd September 1925. Ditto.
22nd September 1925. Died during the night.

(i) Test of innocuousness of glucose solution; (ii) Therapeutic effect of tartar emetic: fatal consequences of administration of full dose during septicæmia.

Horse No. 58. (Plate II.)

27th July 1925. 822 lb. 12 noon. Injected intravenously 82 c.c. of glucose (50% in "normal" saline), at the rate of 100 c.c. per 1000 lb. body weight, to test effects of glucose solution as menstruum for bismuth phosphate. No symptoms.
2nd August 1925. Injected surra blood from rabbit No. 272, showing trypanosomes 20 per field, and simultaneously injected intravenously 41 c.c. of bismuth phosphate suspended in glucose solution (1-4).
8th August 1925. Feeds fairly.
9th August 1925. Conjunctival mucous membrane icteric, few petechiæ.
10th August 1925. Slightly dull, and as above.
12th August 1925. Slight urticaria left side neck, œdema sheath.
13th August 1925. Swelling sheath increased, conjunctival mucous membrane clearer.
14th August 1925. Dull.
16th August 1925. Slightly dull, no changes.
20th August 1925. Feeds fairly, dull.
22nd August 1925. 818 lb. 2-45 p.m. Injected intravenously 40 c.c. M/10 tartar emetic solution, at the rate of 5 c.c. per 100 lb. body weight. After 5 minutes, began to show unsteady gait and lack of control over body, and in a few minutes collapsed and died, exhibiting convulsive movements (opening and closing mouth). Death took place at 3·0 p.m., and just after death the trypanosomes in peripheral blood were reduced to 2 per field.

Therapeutic effect of tartar emetic; fatal consequences of intravenous administration during septicæmia.

Horse No. 47. (Plate II.)

23rd July 1925. 736 lb. 4·0 p.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 148A, showing surra trypanosomes 1 in 5 fields.
28th July 1925. Urticarial eruptions all over body, œdematous swellings both orbits, lips and sheath.
30th July 1925. Urticaria disappeared, œdema eyelids and lips increased, œdema fore legs, breast, and hind legs developing.
31st July 1925. Œdema fore legs increased, others same; muco-purulent discharge left eye.
1st August 1925. Swelling of limbs slightly decreased.
2nd August 1925. Œdema abdomen, legs, and sheath.
3rd August 1925. Œdematous swellings slightly increased in thickness; conjunctival mucous membrane pale and anæmic.
5th August 1925. Bled 25 c.c. from jugular.
9th August 1925. A few petechiæ on conjunctival mucous membrane.
10th August 1925. Slightly dull.
11th August 1925. Dull, feeds fairly.
13th August 1925. Dull, feeds fairly; condition getting worse, eyes sunken and discharging muco-pus; petechiæ on conjunctival mucous membrane.
14th August 1925. Off feed, dull.
15th August 1925. Feeds slowly, dull. 12-30 p.m. Injected only 20 c.c. M/10 tartar emetic intravenously, when commenced to show symptoms of distress; died in about 10 minutes after exhibiting slight convulsive movements.

(i) Tolerance to tartar emetic, intravenous injections, at 5 c.c. M/10 solution per 100 lb. repeated daily for 17 days; (ii) Prophylactic effect same against subcutaneous infection 8 days—nil; (iii) Therapeutic action bismuth sodium tartrate at 1 c.c. of 4 per cent. solution per 100 lb. for 3 days—nil. (iv) Fatal consequences administration tartar emetic during septicæmia.

Horse No. 23. (Plate III.)

18th July 1925. 984 lb. 2-45 p.m. Injected intravenously 50 c.c. M/10 solution tartar emetic.
19th July 1925. 3 p.m. Repeated tartar emetic injection.
20th July 1925. 11 a.m. Repeated tartar emetic injection.
21st July 1925. 12 noon. Repeated injection.
22nd July 1925. 12 noon. Repeated injection.
23rd July 1925. Repeated injection (a little escaped subcutaneously).
24th July 1925. Repeated injection.
25th July 1925. Repeated injection.
26th July 1925. Repeated injection (in the afternoon after the injection the animal went temporarily off feed).
27th July 1925. Repeated injection.
28th July 1925. Repeated injection.
29th July 1925. Ditto.
30th July 1925. Ditto.
31st July 1925. Ditto.
1st August 1925. Ditto.
2nd August 1925. Ditto.
3rd August 1925. Ditto.
7th August 1925. 924 lb.
11th August 1925. 11 a.m. Injected subcutaneously 1 c.c. citrated blood from rabbit 147A, showing trypanosomes 10 per field (" Pony strain ").
21st August 1925. Slightly dull.
28th August 1925. 944 lb. 4-20 p.m. Injected 9·5 c.c. bismuth sodium tartrate solution (4 per cent.) intravenously.
29th August 1925. Repeated above injection (9·5 c.c. bismuth sodium tartrate).
30th August 1925. Repeated above injection. (9·5 c.c. bismuth sodium tartrate).
2nd September 1925. Was injecting intravenously 48 c.c. of M/10 tartar emetic solution, at the rate of 5 c.c. per 100 lb. body weight, but when 35 c.c. had been injected, the animal though cast and secured, became violent, broke casting ropes, and struggled, got up twice and fell down each time, shivering all over body, haggard appearance, emitting gurgling sound from throat, disposition to vomit; lived for 20 minutes apparently in great agony, passed fæces and urine, and then died.

(i) Test of innocuousness of glucose solution; (ii) Tolerance towards bismuth phosphate, injected daily for 10 days; (iii) Prophylactic action of bismuth phosphate; (iv) Therapeutic action of 10 successive injections of full dose of tartar emetic given every 3 days, preceded by a " clearance " with tryparsamide-ineffectual.

Horse No. 48. (Plate III.)

27th July 1925. 868 lb. 3-0 p.m. Injected intravenously 218 c.c. of glucose (50 per cent.) solution in " normal " saline, at the rate of 250 c.c. per 1000 lb. body weight.
1st August 1925. 2-0 p.m. Injected intravenously 21 c.c. bismuth phosphate emulsion in glucose solution (1-4) at the rate of 2·5 c.c. per 100 lb.
2nd August 1925. Repeated bismuth phosphate injection, 21 c.c.
3rd August 1925. Repeated injection.
4th August 1925. Repeated injection.
5th August 1925. Repeated injection.
6th August 1925. Ditto.
7th August 1925. Ditto. 874 lb.
8th August 1925. Ditto.
9th August 1925. Ditto.
10th August 1925. Ditto.
11th August 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 147 C, showing trypanosomes 10 per field.
16th August 1925. Feeds fairly, dull.
18th August 1925. Slightly dull.
22nd August 1925. Feeds fairly, dull, soft fæces.
23rd August 1925. Ditto.

31st August 1925. 820 lb. 3·40 p.m. Injected intravenously 76 c.c. of a 10 per cent. solution of tryparsamide, at the rate of 0·2 c.c. per kilo.
3rd September 1925. 11 a.m. Injected 41 c.c. M/10 tartar emetic solution intravenously.
6th September 1925. Injected intravenously 41 c.c. M/10 tartar emetic.
8th September 1925. 854 lb.
9th September 1925. Injected intravenously 43 c.c. M/10 tartar emetic.
12th September 1925. Repeated injection.
15th September 1925. Ditto.
18th September 1925. Ditto.
21st September 1925. Ditto.
23rd September 1925. 900 lb.
24th September 1925. Repeated M/10 tartar emetic injection, 45 c.c.
27th September 1925. Ditto.
30th September 1925. Ditto.
6th October 1925. Withdrew 20 c.c. of cerebro-spinal fluid, and injected into two guinea-pigs and 1 rabbit.
13th October 1925. 742 lb. About 7 c.c. cerebro-spinal fluid withdrawn and centrifuged; 5 trypanosomes seen in fresh cover glass preparation of sediment.
18th October 1925. 720 lb.
26th October 1925. 740 lb.
28th October 1925. Becoming rather weak in movements, poor condition.
29th October 1925. Looks very poor, weak in movements, and appears generally a pronounced clinical case of surra.
31st October 1925. Very weak in movements and dejected looking.
1st November 1925. Died during the night. Withdrew about 15 c.c. of cerebro-spinal fluid; centrifuged about 7 c.c.; tyrpanosomes present in deposit to the extent of 1 per 5 fields; very distinct leucocytosis.

Therapeutic effect of clearance with "Bayer 205" at 0·5 gram per 1000 lb., followed by tartar emetic injections, on the 2nd, 4th, and 6th days afterwards. Development of fatal paraplegia condition (with death 17 days after last tartar emetic injection).

Horse No. 54. (Plate IV.)

11th August 1925. 846 lb. 11 a.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 147A, showing trypanosomes 10 per field.
17th August 1925. Feeds fairly, slightly dull.
18th August 1925. Ditto.
19th August 1925. Ditto; conjunctival mucous membrane icteric; small gram-sized urticarial eruptions, most common on neck and chest.
20th August 1925. Feeds fairly, dull; conjunctival mucous membrane yellow, urticaria decreased.
22nd August 1925. Slightly dull.
24th August 1925. Feeds fairly.
25th August 1925. Ditto.
28th August 1925. Feeds fairly; conjunctival mucous membrane icteric, with few petechiæ; œdema sheath; urticaria disappeared.
29th August 1925. Feeds fairly. 12 noon. Injected intravenously 0·42 gram "Bayer 205" in 10 per cent. aqueous solution.
30th August 1925. Feeds fairly. 798 lb.
31st August 1925. Feeds fairly. Injected intravenously 40 c.c. of M/10 tartar emetic.
2nd September 1925. Repeated tartar emetic injection.
4th September 1925. Repeated tartar emetic injection.
7th September 1925. 812 lb.
19th September 1925. Developed paraplegia, shows unsteady gait.
20th September 1925. Feeds slowly, sitting and then lying down alternately; can only raise head and fore part of body, but not whole body. 4-22 p. m. Withdrew 15 c.c. cerebro-spinal fluid, and injected intrathecally 16 c.c. of a 0·1 per cent. solution of "Bayer 205." Just after injection there was increased respiration, which gradually became normal, but after about 10 minutes animal began to show symptoms of uneasiness, frequently opening and closing mouth as if yawning, raising neck every now and then, restlessness, pawing with fore legs, eyes staring. At 5 p.m. given injection of chloral hydrate per rectum (3 oz) in ½ gallon warm water after which the animal became quieter, and lay in a semi-conscious condition. 5-30 p.m. Injected intravenously 8·2 c.c. of a 10 per cent. solution "Bayer 205." During the night the animal struggled, and moved itself from one

place to another in its box. Cerebro-spinal fluid was examined microscopically ; centrifuged deposit showed 8 trypanosomes per field ; direct examination, without centrifugation, failed to reveal trypanosomes.

21st September 1925. Off feed, lying down unconscious, moving forelegs now and then, eyes partially closed, respiration deep and increased in rate ; destroyed by chloroform at 11-30 a.m.

(i) Rate of disappearance of trypanosomes from peripheral circulation after intravenous administration " Bayer 205 " at 1 gram per 1000 lb.; (ii) Therapeutic effect of " clearance " with " Bayer 205 " at 1 gram per 1000 lb. and repeated injections, every 3 days, for 5 times, of tartar emetic. Supervention of cerebro-spinal symptoms, with death 2 days after last tartar emetic injection. Trypanosomes present in large numbers in cerebro-spinal fluid at time of death, but not in fluid from serous cavities.

Horse No. 53. (Plate IV.)

2nd August 1925. 868 lb. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 272 showing trypanosomes 20 per field.
7th August 1925. Swelling at seat of injection of surra blood.
8th August 1925. Feeds fairly ; swelling decreased.
9th August 1925. Conjunctival mucous membrane icteric, with few petechiæ.
11th August 1925. Slightly dull ; conjunctival mucous membrane very icteric ; small urticarial eruptions all over body, with tendency to become diffuse.
12th August 1925. Feeds fairly, dull, urticaria decreasing, œdema of all four legs.
13th August 1925. 882 lb. Feeds fairly, dull, urticaria, and œdema all limbs still present ; mucous discharge right eye, with petechiæ on conjunctival mucous membrane.
14th August 1925. Slightly dull, urticaria less marked, and discharge from eye ceased.
16th August 1925. Urticaria reappeared, swelling same as before.
17th August 1925. No change, except less urticaria.
18th August 1925. No change ; urticaria still present.
19th August 1925. Urticarial eruptions have become flattened and diffuse ; conjunctival mucous membrane again more icteric, less injected ; eyes watery.
21st August 1925. 880 lb.
22nd August 1925. Urticaria, and œdema hind legs increased.
23rd August 1925. Urticaria disappeared ; œdema legs, sheath, and belly increased ; few petechiæ on conjunctival mucous membrane.
27th August 1925. 12-15 p.m. Injected " Bayer 205 " intravenously, 0·88 gram in 10 per cent. solution, at the rate of 1 gram per 1000 lb. body weight.
28th August 1925. Movements of trypanosomes very sluggish.
2nd September 1925. Weak.
6th September 1925. Slightly dull, with catarrhal discharge from nostrils.
8th September 1925. 816 lb. Injected 0·82 gram " Bayer 205 " intravenously in 10 per cent. solution.
9th September 1925. Feeds fairly, dull.
11th September 1925. Injected 40 c.c. M/10 tartar emetic solution intravenously.
12th September 1925. Weak.
13th September 1925. 808 lb.
14th September 1925. Repeated tartar emetic injection, 40 c.c.
17th September 1925. Ditto.
20th September 1925. Ditto.
21st September 1925. Feeds fairly.
22nd September 1925. Mucous discharge from both nostrils ; head and neck slightly turned to the right ; right eye partially closed, right ear turned antero-externally, while the left one is turned postero-externally ; slightly dull-looking ; symptoms probably due to slight localized congestion of brain.
23rd September 1925. 770 lb. Condition as yesterday, but eye is a little better ; takes grass but no grain. Injected 40 c.c. M/10 tartar emetic solution intravenously.
25th September 1925. Died suddenly at 7 a.m. Cerebro-spinal fluid was taken 5 hours after death, and after centrifugation the sediment was examined microscopically after staining with Leishman, and was found positive for trypanosomes, which were present in considerable numbers in the smear. Fluids aspirated from pericardial sac, peritoneal, and pleural cavities were centrifuged, and sediment stained with Leishman, but no trypanosomes were seen.

(i) Prophylactic action of tryparsamide against simultaneous subcutaneous infection (nil) ; (ii) The rapeutic action of typarsamide (poor) ; (iii) Therapeutic action of tartar emetic, alternate day in-

jections, three insufficient; (iv) Therapeutic action of tartar emetic (using tryparsamide for clearing) alternate day injections, 10 apparently sufficient.

Horse No. 51. (Plates V and XXIV.)

11th August 1925. 972 lb. Injected intravenously 82·2 c.c. of a 10 per cent. solution of tryparsamide, at the rate of 0·2 c.c. per kilo body weight, and injected subcutaneously 1 c.c. citrated blood from rabbit No. 147A, showing trypanosomes 10 per field.

17th August 1925. Feeds fairly, dull.
18th August 1925. Dull.
22nd August 1925. 896 lb. Injected tryparsamide again at same rate as before.
30th August 1925. 3-45 p.m. Repeated injection.
1st September 1925. 3 p.m. Injected 45 c.c. M/10 tartar emetic solution intravenously.
3rd September 1925. Repeated the last injection,
5th September 1925. Repeated the last injection.
8th September 1925. 988 lb.
13th September 1925. 940 lb.
15th September 1925. 12 noon. Injected 92 c.c. of a 10 per cent. solution of tryparsamide intravenously.
17th September 1925. Injected 47 c.c. M/10 solution tartar emetic intravenously.
19th September 1925. Repeated tartar emetic injection, 47 c.c.
21st September 1925. Repeated tartar emetic injection, 47 c.c.
23rd September 1925. Ditto Ditto. 980 lb.
25th September 1925. Repeated tartar emetic injection, 49 c.c.
27th September 1925. Ditto.
28th September 1925. Cerebro-spinal fluid examined centrifuged and not centrifuged, in fresh and stained smears, and found negative for trypanosomes.
29th September 1925. Repeated tartar emetic injection, 49 c.c.
1st October 1925. Repeated injection, 49 c.c.
3rd October 1925. Ditto.
5th October 1925. Ditto.
6th October 1925. 20 c.c. of cerebro-spinal fluid withdrawn, and inoculated subcutaneously to two guinea-pigs and one rabbit.
26th October 1925. 973 lb.
22nd November 1925. 980 lb.
29th November 1925. 990 lb.
5th December 1925. Commenced to exhibit maniacal symptoms,—breaking attachment in stable, bleeding from gums through struggling, then lying down. Cast, withdrew into each of 3 test tubes about 15 c.c. of cerebro-spinal fluid, quite clear, no trypanosomes discoverable in centrifuged deposit on prolonged examination. Also withdrew blood from jugular into citrate solution, equal parts. Inoculated one lame mule with 15 c.c. of the cerebro-spinal fluid, and one lame pony with 15 c.c. of the citrated blood (no trypanosomes appeared in these animals upon daily examination subsequently).
6th December 1925. No symptoms of excitement; looks quite calm and comfortable, feeds fairly.
7th December 1925. Feeds fairly.
20th December 1925. 984 lb.
27th December 1925. 986 lb.
2nd January 1926. 986 lb.
9th January 1926. 980 lb.

Weekly weights in pounds after this date were as follows:—
958, 940, 978, 944, 950, 1008, 980, 1088, 936, 936, 936, 930, 964, 984, 942, 912, 930, 962, 968, 936, 988, 952, 950, 960, 965, 952, 952, 952, 960, 970, 969, 968, 964, 944, 952, 960, 970, 960, 968, 964, 944, 952, 948, 976, 980, 972, 956, 965, 970, 972, 980, 980, 998, 996, 994. The animal remained well except for œdema on chest from 10th September to 17th September 1926. It was discharged in good condition on 16th December 1926. (See Photographs.)

Therapeutic action of "Bayer 205" at 1 gram per 1000 lb. intravenously. Compare Horse 3 at 2·5 grams, and Mare 2 at 5 grams.

Horse No. 19. 924 lb. (Plate VI.)

15th July 1925. 3 p.m. Injected about 1 c.c. citrated blood from rabbit No. 143A swarming with trypanosomes.
20th July 1925. Feeds fairly.

21st July 1925. Feeds fairly; membrana nictitans slightly injected.
22nd July 1925. Feeds fairly.
23rd July 1925. Ditto.
24th July 1925. Ditto; slight œdema hind legs, and urticarial eruptions especially on hind quarters.
25th July 1925. Feeds fairly; increased respiration, with abdominal type of breathing.
26th July 1925. Œdema and urticaria still present; breathing normal.
27th July 1925. Ditto.
28th July 1925. Urticaria nearly disappeared.
30th July 1925. Slight œdema hind legs present.
31st July 1925. No change.
5th August 1925. 870 lb. 11 a.m. Injected intravenously 0·87 gram "Bayer 205" in 10 per cent. aqueous solution, at the rate of 1 gram per 1,000 lb. body weight. Bled 40 c.c. blood from jugular vein at 3 p.m.
6th August 1925. Small number of trypanosomes still present; urticaria appears on head.
7th August 1925. No clinical change.
10th August 1925. No urticaria; animal looks better.
13th August 1925. 840 lb.
19th August 1925. Increased respiration.
20th August 1925. Respiration 28 per minute, and of "double" type.
25th August 1925. Feeds fairly, lying down, pulse 80, respiration 20 per minute, and expiration of "double" type.
26th August 1925. Feeds fairly, lying down.
27th August 1925. Ditto.
28th August 1925. Off feed, lying down, condition bad. Injected intravenously 42 c.c. of a 10 per cent. solution of "Bayer 205," at the rate of 5 grams per 1,000 lb. body weight. Died during the night.

Therapeutic effect of a single intravenous administration of "Bayer 205" at 2·5 grams per 1,000 lb. body weight; acute fatal cerebro-spinal involvement ensues in one month.

Horse No. 3. (Plate VI.)

15th July 1925. 896 lbs. 3 p.m. Injected subcutaneously ab ut 1 c.c. citrated blood swarming with trypanosomes from rabbit No. 143A.
20th July 1925. Feeds fairly.
21st July 1925. Feeds fairly; membrana nictitans slightly injected.
22nd July 1925. Feeds fairly.
24th July 1925. Small urticarial eruptions appearing on body.
26th July 1925. Slight œdema of hind legs; eruptions still present.
27th July 1925. Ditto. ditto.
28th July 1925. Urticaria decreasing; œdema still present.
30th July 1925. Only slight œdema of hind legs present.
31st July 1925. No change.
2nd August 1925. Urticaria and slight œdema.
5th August 1925. 868 lb. 11 a.m. Injected intravenously 2·17 grams "Bayer 205" in 10 per cent. aqueous solution, at the rate of 2·5 grams per 1,000 lb. body weight. At 3 p.m., took 25 c.c. blood from jugular vein.
6th August 1925. Urticaria increased on neck.
7th August 1925. Urticaria decreased.
10th August 1925. Urticaria and œdema disappeared; animal getting better in appearance.
13th August 1925. 864 lb.
15th August 1925. Blood examination showed one microfilaria per specimen.
2nd September 1925. Blood examination showed one microfilaria per specimen.
3rd September 1925. Dull, lies in sitting position. Sat down last night and could not get up. Appears to have developed paraplegia; tries to get up by means of fore legs, but does not seem to have strength enough in hind legs to enable it to get up. Frequently remains sitting like a dog, resting on one of fore legs and chest, with hind legs turned to one side of the body. Conjunctival mucous membrane slightly injected. Takes grain and grass normally. Urine and fæces normally passed. Paralysis of hind quarters appears to affect both motor and sensory nerves.
4th September 1925. Feeds fairly, dull, lying down.
3-20 p.m. Blood negative for trypanosomes. About 40 c.c. of cerebro-spinal fluid withdrawn, and about half this quantity was centrifuged for 15 minutes. Sediment on examination under the microscope was found to be swarming with trypanosomes. Cerebro-spinal fluid was somewhat cloudy during first part of flow and then became clear.

3-34 p.m. Injected intrathecally 2 c.c. of a 10 per cent. solution of " Bayer 205 ". About 10 minutes after injection, lay prostrate on side, struggling with fore legs.

5-20 p.m. Had now developed spasmodic convulsions, staring eyeballs, twitching of upper eyelid, hurried respiration, with occasional forced respiration, neighing, contraction of the muscles of prehension and mastication, with occasional movement of jaws, as if hurriedly eating something. These symptoms were intermittent, arising at intervals of 5 to 10 minutes, but struggling with fore legs was continuous.

6 p.m. Animal was delirious, neighing now and again. About 20 c.c. of blood was taken from jugular vein and after defibrination mixed with an equal quantity of distilled water and centrifuged for 15 minutes; no trypanosomes found in sediment on examination. Died.

(Citrated blood was injected subcutaneously into 3 guinea-pigs, Nos. 153, 154 and 155, in quantities of 1 c.c. each. Guinea-pigs were kept under observation till 23rd September 1925, and daily examination of blood for trypanosomes during this period proved negative.)

(1) Therapeutic action of " Bayer 205 " given intravenously alone at 5 grams per 1,000 lb. Supervention of acute paraplegic symptoms; (ii) Therapeutic action of " Bayer 205 " intravenously—intrathecally of no avail *in extremis*.

Mare No. 2. (Plate VII.)

15th July 1925. 906 lb. 3 p.m. Injected subcutaneously 1 c.c. of citrated blood from rabbit 143A swarming with trypanosomes. Watery discharge from left eye.

17th July 1925. Eye better.

18th July 1925. Eye recovered.

20th July 1925. Feeds fairly.

21st July 1925. Membrana nictitans slightly anæmic.

24th July 1925. Slight œdema hind legs, dull-looking, slight urticarial eruptions over shoulders and sides of body.

25th July 1925. Urticaria and œdema present; a few small pin-head petechiæ on conjunctival mucous membrane.

26th to 28th July 1925. Ditto ditto ditto.

30th July 1925. Only slight œdema of hind legs present.

31st July 1925. No change.

2nd August 1925. No urticaria, slight œdema.

5th August 1925. 852 lb. Injected intravenously 4·16 grams " Bayer 205 " in 10 per cent. watery solution, at the rate of 5 grams per 1,000 lb. Bled 25 c.c. from jugular. 3 p.m. Trypanosomes still present.

6th August 1925. Feeds fairly, dull, Urticarial eruptions all over body; severe œdema lips, eyelids, and cheeks; dull.

7th August 1925. Œdema and urticaria much reduced; slightly dull, feeds fairly.

8th August 1925. Slightly dull, œdema of lips, face and eyelids disappeared and also most of the urticaria.

9th August 1925. Conjunctival mucous membrane anæmic; slight œdema belly and chest.

13th August 1925. 808 lb.

16th August 1925. Looks better, conjunctival mucous membrane improved, and œdema and urticaria disappeared.

8th September 1925. 888 lb.

13th September 1925. 888 lb.

21st September 1925. Feeds fairly, dull, lying down; groaning a little; sometimes sits down like a dog and sometimes lies down on side.

5 p.m. Injected 9 c.c. of a 10 per cent. solution of " Bayer 205 " intravenously and 9 c.c. of a 0·1 per cent. solution of " Bayer 205 " intrathecally. After the injection, the animal began eating grass normally, but was unable to sit down since 3 p.m. No symptoms of intoxication due to the " Bayer 205 " were seen after the injection, the animal remaining in the same condition as before. During the night the mare remained in the same condition, now and again raising the head, but could not keep it up, and it fell down on ground. Fæces and urine passed normally.

22nd September 1925. Off feed, lying down. At 9 a.m., the mare was in the same condition as last evening; fæces and urine normal; groaning has slightly increased; does not appear to be in full possession of senses. 4 p.m. No change in condition except that mare looks somewhat more calm; ate a little grass.

23rd September 1925. No change in condition; struggling with fore legs. Off feed completely. Died later, during the night.

(i) Prophylactic action "Bayer 205" at 1 gram per 1,000 lb. body against simultaneous subcutaneous infection; (ii) Therapeutic effect "Bayer 205", combined treatment, intravenously, at 5 grams per 1,000 lb. and intrathecally at 20 c.c. of 0·1 per cent. solution per 1,000 lb. Relapsed. Treated again but died later from Bayer intoxication while in low condition.

Mare No. 57. (Plate VII.)

2nd August 1925. 912 lb. Inoculated subcutaneously with 1 c.c. citrated blood from rabbit No. 272, showing trypanosomes 20 per field and simultaneously injected intravenously 0·9 gram of Bayer 205" in 10 per cent. solution, at the rate of 1 gram par 1,000 lb. body weight.
8th September 1925. 900 lb.
13th September 1925. 904 lb.
23rd September 1925. 890 lb.
5th October 1925. Injected subcutaneously 1 c.c. citrated surra blood from rabbit No. 284.
11th October 1925. 850 lb.
15th October 1925. Feeds fairly.
17th October 1925. Fæces soft; œdema hind legs up to hocks.
18th October 1925. 840 lb. Ditto ditto.
19th October 1925. Fæces soft; œdema increasing.
20th October 1925. Ditto. ditto.
21st October 1925. Fæces soft; week, œdema decreasing.
22nd October 1925. Feeds fairly, dull; weak; œdema decreasing.
23rd October 1925. Ditto ditto.
24th October 1925. Ditto ditto.
25th October 1925. 784 lb. Ditto.
26th October 1925. Showed marked weakness of hind quarters, wasting, and dullness. Injected 15·6 c.c. of a 0·1 per cent. solution of "Bayer 205" intrathecally, and 39·2 c.c. of a 10 per cent. solution intravenously (cerebro-spinal fluid flowed away readily at the beginning, was quite clear, but injection performed later not surely done). Centrifuged about 10 c.c. of the clear cerebro-spinal fluid; deposit showed very few red cells, but trypanosomes were present to the extent of 5 in one specimen.
27th October 1925. Marked weakness of hind quarters; feeds fairly; dull.
28th October 1925. Ditto ; marked swaying of hind legs in walking.
29th October 1925. Ditto.
1st November 1925, Ditto.
2nd November 1925. Very weak, and in very poor condition.
3rd November 1925. Ditto.
7th November 1925. Ditto.
8th November 1925. Very weak in movements; œdema under belly.
9th to 12th November 1925. Improving appreciably.
13th November 1925. Still improving; rather weak in movements; œdema belly.
14th to 18th November 1925. Ditto.
19th November 1925. Recovered.
22nd November 1925. 824 lb. Weak.
23rd November 1925. Condition fair.
24th November to 15th December 1925. Condition fair.
29th November 1925. 820 lb.
6th December 1925. 826 lb.
11th December 1925. 770 lb.
16th December 1925. Feeds fairly; becoming rather weak in condition, and shows weakness of hind quarters.
18th December 1925. 784 lb. Ditto ditto.
19th December 1925. Ditto ditto ditto.
21st December 1925. 784 lb. Condition rather poor, but much better than it was at the time of treatment. Injections, intravenous and intrathecal, of 26th October 1925, repeated.
22nd December 1925. Slight laminitis and marked weakness of hind quarters
23rd December 1925. Ditto.
24th December 1925. Weakness of hind quarters.
25th December 1925. 790 lb. Ditto.
1st January 1926. 792 lb.
9th January 1926. 822 lb.
16th January 1926. 818 lb,
23rd January 1926. 824 lb. Weak.

27th January 1926. Gave one pound of boiled linseed with grain.
31st January 1926. Lying down.
1st February 1926. Feeds fairly; lying down prostrate, struggling with fore feet from time to time. Withdrew cerebro spinal fluid; microscopical examination of centrifuged deposit showed no trypanosomes and fluid otherwise normal—no distinct excess of leucocytosis; few red cells. 20 c.c. blood taken for rabbit and guinea-pig inoculation, and blood examination was negative until time of death. Result negative.
2nd February 1926. Died of suspected schistosomiasis at 7-30 a.m.

(i) Prophylactic action of "Bayer 205" administered intravenously at 5 grams per 1,000 lb. against simultaneous subcutaneous infection, successful; (ii) Therapeutic treatment (moderate case) with "Bayer 205" administered alone at 5 grams per 1,000 lb. apparently successful.

Horse No. 46. (Plates VIII and XXIV.)

23rd July 1925. 856 lb. 4 p.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 148A, showing trypanosomes 1 in 5 fields, and simultaneously injected intravenously 4·5 grams "Bayer 205" in aqueous solution, at the rate of 5 grams per 1,000 lb. body weight.
1st August 1925. Swelling at seat of injection of surra blood left side neck.
2nd August 1925. Swelling increased in size.
9th August 1925. Swelling subsided.
13th August 1925. 826 lb.
8th September 1925. 889 lb.
13th September 1925. 884 lb.
16th September 1925. Shows symptoms of colic; administered colic drench and enema of soap and water.
23rd September 1925. 860 lb.
5th October 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit 291, showing trypanosomes 1 per specimen.
11th October 1925. 866 lb.
16th October 1925. Œdema both hind legs.
17th October 1925. Ditto ditto.
18th October 1925. 860 lb.
19th October 1925 to 24th October 1925. Œdema decreasing.
25th October 1925. 856 lb.
30th October 1925. Becoming rather weak.
6th November 1925. 812 lb.
9th November 1925. Œdema sheath.
12th November 1925. Weak in movements, œdema sheath.
13th November 1925. Showed moderate clinical symptoms of surra—not so marked as in the case of the other horses treated similarly to-day. Injected intravenously 40·6 c.c. of a 10 per cent. solution of "Bayer 205" (operation not completely successful, owing to blunted needle). Withdrew cerebro-spinal fluid; much blood, but no trypanosomes visible in centrifuged deposit. Very unsteady on getting up.
14th November 1925. Feeds fairly; œdema sheath and belly; very slight laminitis (also rope gall left hind pastern).
15th November 1925. Feeds fairly, and other symptoms as yesterday.
16th November 1925. Ditto.
17th November 1925 Ditto.
18th November 1925. Ditto. (Rope injury aggravated.)
19th to 25th November 1925. Ditto.
26th November 1925. Abscess formed left hock, which is opened.
27th November 1925. Tested by intrapalpebral mallein test for glanders; result apparently negative.
29th November 1925. 864 lb.
6th December 1925. 866 lb.
13th December 1925. 866 lb.
20th December 1925. 860 lb.
27th December 1925. 862 lb.
3rd January 1926. 822 lb.

Weekly weight in pounds after this date were as follows:—

826, 784, 798, 824, 790, 800, 826, 780, 784, 804, 802, 796, 792, 794, 824, 800, 800, 800, 816, 794, 804, 804, 798, 800, 796, 800, 800, 804, 800, 804, 812, 804, 830, 818, 798, 814, 795, 800,

816, 810, 800, 798, 806, 812, 830, 845, 825, 825, 840, 846. The animal did not relapse, fed well and was discharged in good condition on 16th December 1926. (See Photographs.)

(i) Prophylactic action "Bayer 205" at 5 grams per 1,000 lb. against infection 3 days later—successful; (ii) Therapeutic effect of combined treatment with "Bayer 205",—intravenously at 5 grams per 1,000 lb. and intrathecally at 20 c.c. of 0·1 per cent. solution per 1,000 lb.—single administration.

Horse No. 21B. (Plate VIII.)

20th July 1925. 12 noon. Injected intravenously 4 grams "Bayer 205" in 10 per cent. aqueous solution, at the rate of 5 grams per 1,000 lb. body weight.
21st July 1925. Marked urticarial eruptions appear all over body, notably head, neck, shoulder, and chest, mostly scattered and discrete and from the size of 2 to 4 anna pieces, but some diffuse and coalesced to form swellings about 1 to 2 inches long and 6 inches broad on chest.
22nd July 1925. Above eruptions still present, but show tendency to decrease in size.
23rd July 1925. Urticaria entirely disappeared. 4-0 p.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 148A showing trypanosomes 1 in 5 fields.
1st August 1925. Hard swelling at seat of injection with surra blood, 3 by 4 inches.
5th August 1925. Swelling decreasing.
13th August 1925. 880 lb.
8th September 1925. 920 lb.
13th September 1925. 930 lb.
23rd September 1925. 962 lb.
5th October 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 291, showing trypanosomes 1 per specimen.
11th October 1925. 879 lb. Feeds fairly.
18th October 1925. 880 lb.
23rd October 1925. Œdema appearing on sheath.
25th October 1925. 929 lb.
26th October 1925. Œdema sheath increasing.
4th November 1925. Œdema sheath, abdomen, and breast.
5th November 1925. Moves rather stiffly; œdema abdomen and breast.
6th November 1925. 850 lb. Ditto.
7th November 1925. Fairly good conditon, but moves rather stiffly. Injected intravenously 42·5 c.c. of a 10 per cent. solution of "Bayer 205" and 17 c.c. of 0·1 per cent. solution "Bayer 205" intrathecally. Withdrew about 5 c.c. of clear cerebro-spinal fluid; centrifuged; deposit shows very few red cells, trypanosomes present to the extent of 2 or 3 per field. After injection, the horse showed nervous uneasiness, lay down for half an hour after injection, showing uneasiness, and trying to get up by means of fore legs, and exhibiting lack of power in hind legs as if affected with paraplegia. Died.

(i) Prophylactic treatment with "Bayer 205" intravenously at 7·5 grams per 1,000 lb. against subcutaneous infection 3 weeks later—successful; (ii) Therapeutic effect "Bayer 205", combined intravenous—intrathecal treatment.

Horse No. 26. (Plates IX and XXIV.)

20th July 1925. 800 lb. 12 noon. Injected intravenously 6 grams of "Bayer 205" in 10 per cent. solution, at the rate of 7·5 grams per 1,000 lb. body weight.
21st July 1925. Pea-sized urticarial eruptions scattered over body, especially in region of head, shoulders, and thighs, slight œdema upper eyelids, sheaths and lip commissures, and to some extent above hoofs.
22nd July 1925. Above symptoms decreasing.
23rd July 1925. Urticaria and œdema disappeared.
7th August 1925. 808 lb.
11th August 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 147A, showing trypanosomes 10 per field.
29th August 1925. 4 p.m. Bled 50 c.c. blood from jugular vein and injected subcutaneously into dog 38. (Dog was kept under observation until 23rd September 1925, but no trypanosomes were discoverable during this period in daily examination of its blood.)
8th September 1925. 860 lb.
23rd September 1925. 858 lb.
5th October 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 284 showing trypanosomes 1 per specimen.

11th October 1925. 842 lb.
16th October 1925. Œdema both hocks, both knees, and sheath.
17th and 18th October 1925. Ditto.
18th October 1925. 840 lb.
19th to 22nd October 1925. Œdema decreasing.
23rd October 1925. Feeds fairly, dull, œdema decreasing.
24th October 1925. Ditto.
25th October 1925. 812 lb.
26th October 1925. Œdema decreasing.
28th October 1925. Œdema increasing.
30th October 1925. Becoming rather weak.
3rd November 1925. Œdema sheath and belly.
4th November 1925. Œdema sheath and belly.
5th November 1925. Ditto. Weak in movements.
6th November 1925. 784 lb. Had fallen down during night, and bruised skin, with appearance of bed sores.
7th November 1925. Injected 39·2 c.c. of 10 per cent. solution of " Bayer 205 " intravenously and 15·6 c.c. of 0·1 per cent. solution intrathecally. Withdrew about 5 c.c. cerebro-spinal fluid, slightly turbid, deposit shows number of red cells, no trypanosomes and no leucocytes. Fell down at night and had a number of bed sores.
8th November 1925. Very weak in movements, dull, feeds fairly, poor condition; œdema sheath and belly.
9th to 11th November 1925. Ditto ditto.
12th November 1925. Improving.
13th to 14th November 1925. Improving. 736 lb.
15th November 1925. Much improved.
22nd November 1925. 738 lb.
29th November 1925. 744 lb.
6th December 1925. 782 lb.
13th November 1925. 784 lb.
19th December 1925. 780 lb.
27th December 1925. 784 lb.
3rd January 1926. 796 lb.
10th January 1926. 798 lb.
17th January 1926. 766 lb.
24th January 1926. 798 lb.

Weekly weights in pounds after this date were as follows :—
778, 766, 770, 780, 774, 772, 752, 756, 788, 762, 812, 788, 800, 850, 830, 842, 810, 822, 840, 822, 830, 830, 825, 812, 816, 818, 824, 832, 822, 840, 834, 822, 822, 820, 824, 830, 825, 818, 830, 822, 816, 804, 810, 798, 820, 824. The animal did not relapse, fed well and was in excellent condition when discharged on 16th December 1926. (See Photographs.)

(i) Prophylactic action " Bayer 205 " at 10 grams per 1,000 lb. against subcutaneous infection (22nd September 1925) 2 months later—not complete; (ii) Therapeutic effect " Bayer 205 " combined treatment intravenously at 5 grams per 1,000 lb. and intrathecally at 20 c.c. of 0·1 per cent. solution per 1,000 lb. (13th November 1925). Relapse. Treatment repeated 21st December 1925 (successful).

Horse No. 28. (Plates X and XXIV.)

20th July 1925. 756 lb. 12 noon. Injected intravenously 7·5 grams " Bayer 205 " in aqueous solution, at the rate of 10 grams per 1,000 lb. body weight.
21st July 1925. Isolated, scattered, small urticarial eruptions. especially on the head and abdomen, each about the size of gram seed; slight œdema upper eye-lids, sheath, and commissures of lips.
22nd July 1925. Above external symptoms decreasing.
23rd July 1925. Urticaria and œdema disappeared.
24th July 1925. Left knee swollen, with discharge of sanguineous fluid from a wound.
25th July 1925. Albumen in urine rising to 1 gram per litre.
26th July 1925. Shows symptoms of laminitis in walking, in both hind legs and to some extent, both fore legs. Albumen present to extent of ½ gram per litre.
27th July 1925. Laminitis as before.
29th July 1925. Laminitis a little better; no albumen in urine.
4th August 1925. Can walk out of stable now with little trouble.

7th August 1925. 732 lb.
9th September 1925. 856 lb.
22nd September 1925. 2-15 p.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 270, showing trypanosomes 25 per field. (Control Horse 65 injected in same manner, died on 29th September 1925, acute infection.)
27th September 1925. 790 lb.
11th October 1925. 742 lb. Feeds fairly.
18th October 1925. 744 lb.
24th October 1925. Œdema sheath.
25th October 1925. 800 lb. Œdema sheath increasing.
26th October 1925. Ditto.
28th October 1925. Œdema decreasing.
29th October 1925. Ditto.
30th October 1925. Becoming rather weak.
31st October 1925. Œdema sheath.
4th November 1925. Œdema sheath and belly.
5th to 11th November 1925. Œdema sheath and belly. 740 lb. on 6th November 1925.
13th November 1925. Fairly weak, thin condition; distinct clinical case of surra. Injected 37 c.c. of a 10 per cent. solution "Bayer 205" intravenously, and 14·8 c.c. of a 0·1 per cent. solution "Bayer 205" intrathecally. Withdrew about 10 c.c. of quite clear cerebro-spinal fluid, centrifuged; only 4 trypanosomes seen in deposit, very few red cells.
14th November 1925. 714 lb. Very slight laminitis, and œdema on sheath and belly.
15th November 1925. Ditto.
16th November 1925. Recovered from laminitis; œdema sheath.
17th to 19th November 1925. Œdema sheath.
20th to 22nd November 1925. Œdema sheath and belly. 738 lb. on the 22nd.
23rd to 25th November 1925. Œdema decreasing.
26th November 1925. Recovered.
12th December 1925. 720 lb.
18th December 1925. 714 lb.
21st December 1925. Very poor-looking, thin, and rather weak in movements. Repeated "Bayer 205" injections of 13th November 1925, both intrathecal and intravenous.
22nd December 1925. Laminitis, and swelling at seat of inoculation into jugular vein.
23rd December 1925. Laminitis, and œdema breast.
24th December 1925. Slight laminitis, and œdema breast.
25th December 1925. 690 lb. Slight laminitis.
26th December 1925. Ditto.
1st January 1926. 680 lb.
9th January 1926. 708 lb.
16th January 1926. 699 lb.

Weekly weights in pounds after this date were as follows:—
704, 700, 706, 704, 704, 699, 704, 716, 708, 694, 706, 700, 756, 756, 750, 756, 792, 780, 770, 796, 766, 770/776, 770, 780, 784, 780, 790, 800, 810, 812, 800, 798, 790, 792, 796, 796, 800, 796, 775, 792, 808, 804, 808, 808. The animal remained cured and was discharged in good condition on 16th December 1926. (See Photographs.)

(i) Prophylactic effect of tartar emetic administered intravenously simultaneously with infection subcutaneously; (ii) Therapeutic effect of "Bayer 205" administered intravenously and intrathecally in advanced infection—inefficacious.

Horse No. 45. (Plate X.)

23rd July 1925. 878 lb. Injected subcutaneously 1 c.c. of citrated blood from rabbit No. 148-A, showing surra trypanosomes 1 in 5 fields, and simultaneously injected intravenously 87 c.c. M/10 tartar emetic solution, at 4 p.m.
13th August 1925. 852 lb.
17th August 1925. Dull.
8th September 1925. 900 lb.
13th September 1925. 906 lb.
23rd September 1925. 896 lb.
5th October 1925. Injected subcutaneously 1 c.c. of citrated blood from rabbit No. 291 showing 1 trypanosome per specimen.
11th October 1925. 851 lb.
18th October 1925. 848 lb.

19th October 1925. Slight œdema in hind legs.
25th October 1925. 855 lb.
26th October 1925. Œdema decreasing.
30th October 1925. Becoming somewhat weak.
2nd November 1925. Slightly dull.
4th November 1925. Weak and dull.
5th November 1925. Feeds fairly; weak in movements, dull.
7th November 1925. Estimated weight 800 lb., very weak (could not walk to weighing shed to be weighed). Injected 40 c.c. of 10 per cent. solution "Bayer 205" intravenously and 16 c.c. of 0·1 per cent. solution "Bayer 205" intrathecally. About 10 c.c. of water clear cerebro-spinal fluid withdrawn; centrifuged; deposit showed no red cells, but number of white cells; trypanosomes present to the extent of 3 or more per field. Lay down after injection, got up after half an hour.
8th November 1925. Very weak in movements, legs sway from side to side, very weak and dull in appearance, feeds fairly, œdema sheath.
9th November 1925. Ditto.
10th November 1925. Ditto.
11th November 1925. Feeds fairly, lying down, very weak and dull, œdema sheath; sometimes gets up after taking a few wisps of hay, then lies down again.
12th November 1925. Off feed, lying down, very weak, cannot raise head, and shows symptoms of uneasiness.
13th November 1925. Had died during the night of 12th November 1925.

(i) Toxic and prophylactic action of bismuth phosphate; (ii) Therapeutic action of repeated small doses "Bayer 205" (1 gram per 1,000 lb.) administered three times at each recurrence of trypanosomes in 11 days and again in 9 days;—ineffectual.

Horse No. 59. (Plate XI.)

30th July 1925. 1,074 lb. 4 p.m. Injected intravenously 54 c.c. bismuth phosphate (1-4) in glucose solution, at the rate of 5 c.c. per 100 lb. body weight.
31st July 1925. 3-30 p.m. Injected 54 c.c. bismuth phosphate emulsion; appreciable swelling along course of jugular vein and below it.
1st August 1925. Repeated injection of bismuth phosphate, but after injecting 35 c.c. the horse began to show toxic symptoms, and stopped further injection. Horse became affected with trembling and heavy breathing (respiration 70 per minute) which continued for half an hour; did not fall down, and subsequently recovered.
2nd August 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit 272, showing trypanosomes 20 per field.
9th August 1925. Conjunctival mucous membrane icteric, few petechiæ.
10th August 1925. Slightly dull.
13th August 1925. 880 lb. Conjunctival mucous membrane a little less icteric.
16th August 1925. No change.
19th August 1925. Conjunctival mucous membrane not icteric, œdema sheath.
22nd August 1925. 980 lb. 3 p.m. Injected intravenously 1 gram "Bayer 205" in 10 c.c. distilled water, at the rate of 1 gram per 1,000 lb. body weight.
23rd August 1925. 6 a.m. Movement of trypanosomes considerably slower. 9-30 a.m. Trypanosomes appear active in movement.
27th August 1925. Œdema of sheath had disappeared, and that of hind legs decreased.
2nd September 1925. 900 lb. 2 p.m. Injected intravenously 1 gram "Bayer 205" in 10 c.c. distilled water.
8th September 1925. 900 lb.
11th September 1925. Injected 9 c.c. of a 10 per cent. solution of "Bayer 205" intravenously.
12th September 1925. Conjunctival mucous membrane rather pale, with few petechiæ.
13th September 1925. 870 lb.
14th September 1925. Weak. Shows somewhat unsteady gait, much emaciated, œdema hind legs, conjunctival mucous membrane pale.
15th September 1925. Weak.
16th September 1925. Ditto.
17th September 1925. Ditto.
18th September 1925. Very weak; sitting down.
19th September 1925. Dull, lying down, can sit in same posture as a dog for a while, feeds fairly.
20th September 1925. Lying down, unable to sit, in bad condition, muco-purulent discharge from eyes, off feed. 4 p.m. Withdrew 15 c.c. cerebro-spinal fluid, and injected intrathecally 17 c. c. of a 1 per cent. solution of "Bayer 205" followed by 8 c.c. of normal

saline solution to wash down all the drug from the needle. Just after the injection, respiration increased, but after two minutes became normal. No other symptoms of "Bayer" poisoning. Cerebro-spinal fluid examined under microscope both centrifuged and not centrifuged and found negative for trypanosomes. Two guinea-pigs, Nos. 168 and 169, were injected subcutaneously with this fluid. 5-30 p.m. Injected intravenously 8·7 c.c. of a 10 per cent. solution of "Bayer 205." Animal lay down quietly afterwards pawing now and again. Died during the night.

(i) Tolerance to and toxic effect of bismuth phosphate; (ii) Prophylactic acton of bismuth phosphate against subcutaneous infection one day later; (iii) Rate of disappearance of trypanosomes from blood after intravenous injection of "Bayer 205" at 1 gram per 1,000 lb.; (iv) Exhibition of development of "drug-fastness" to "Bayer 205" at 1 gram per 1,000 lb. (3 injections). Death.

Horse No. 59. (Plate XI.)

30th July 1925. 1,074 lb. Injected intravenously 54 c.c. bismuth phosphate emulsion in glucose solution (1-4), at the rate of 5 c. c. per 100 lb. body weight.
31st July 1925. Injected intravenously bismuth phosphate emulsion as before; appreciable swelling along course of jugular vein.
1st August 1925. 3 p.m. Was injecting bismuth phosphate emulsion as before, but after injecting 35 c.c. the horse began to show toxic symptoms; stopped injection. Showing heavy breathing (respiration 70 per minute), trembling; did not fall down; subsequently recovered.
2nd August 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 272, showing trypanosomes 20 per field.
9th August 1925. Conjunctival mucous membrane icteric, with few petechiæ.
10th August 1925. Slightly dull.
11th August 1925. Ditto.
12th August 1925. Ditto.
13th August 1925. Ditto, conjunctival mucous membrane a little less icteric.
16th August 1925. Ditto.
19th August 1925. Conjunctival mucous membrane not icteric; œdema sheath.
22nd August 1925. 980 lb. 3 p.m. Injected 1 gram "Bayer 205" in 10 per cent. solution intravenously.
23rd August 1925. 6 a.m. Movement of trypanosomes considerably slower. 9-30 a.m. Trypanosomes in active movement.
27th August 1925 Œdema of sheath disappeared, and that of hind legs reduced.
2nd September 1925. 900 lb. 2 p.m. Injected 1 gram "Bayer 205" in 10 per cent. solution intravenously.
8th September 1925. 900 lb.
11th September 1925. 1 p.m. Injected 0·9 gram "Bayer 205" in 10 per cent. solution intravenously.
12th September 1925. Conjunctival mucous membrane slightly pale, with a few petechiæ.
13th September 1925. 870 lb.
14th September 1925. Weak; somewhat unsteady gait; much emaciated; œdema hind legs; conjunctival mucosa anæmic.
15th to 17th September 1925. Weak.
18th September 1925. Very weak; sitting and lying down.
19th September 1925. Feeds fairly; dull; lying down, but can sit down like a dog for a while.
20th September 1925. Off feed, lying down, unable to sit, remains prostrate inside, in very bad condition; muco-purulent discharge from eyes. Died.

(i) Prophylactic action tartar emetic, 3 daily injections intravenously at 5 c.c. M/10 solution per 100 lb. body weight,—insufficient to prevent development of infection when virulent inoculation was performed 24 hours afterwards, but affection distinctly milder than in control and horses injected with virulent blood after 3 and 5 days in same test; (ii) Curative action "Bayer 205" at 5 grams per 1,000 lb. body weight intravenously alone, repeated after a month's interval,—apparently completely effective, with this relatively mild type of infection; (iii) Test of Kligler and Weitzman's contention that trypanosomes lose virulence in blood prior to their disappearance after "Bayer" injection,—not confirmed; guinea-pigs developed infection after inoculation during whole time when blood was found to contain trypanosomes on microscopical examination.

Horse No. 64. (Plates XI and XXIV.)

1st September 1925. 1,060 lb. Injected intravenously 3 c.c. M/10 solution tartar emetic at rate of 5 c.c. per 100 lb. body weight.
2nd September 1925. Repeated injection.

3rd September 1925. Repeated injection.
4th September 1925. Injected 1 c.c. citrated blood from rabbit No. 230-A, showing trypanosomes 6 per field.
7th September 1925. 1,062 lb.
12th September 1925. Conjunctival mucous membrane icteric.
16th September 1925. Œdema hind legs.
24th September 1925. 1,123 lb. 9 a.m. Injected 56 c.c. of a 10 per cent. solution of "Bayer 205" intravenously, at the rate of 5 grams per 1,000 lb. body weight, and subinoculated, subcutaneously, two guinea-pigs with jugular blood.
12 noon. Subinoculated two guinea-pigs.
3 P.M. Ditto.
9 P.M. Ditto.
25th September 1925. 9 a.m. Subinoculated two guinea-pigs. Considerable œdema of the upper and lower lips, angle of the mouth, upper and lower lids of both eyes and sheath. Œdema hind legs increased. Slight urticaria all over body and particularly over hind parts.
26th September 1925. Œdema of lips and eye lids decreased, but that of sheath considerably increased. Symptoms of laminitis on both hind legs.
27th September 1925. 1,148 lb. Œdema of lips and eye lids disappeared but that of sheath unchanged. Laminitis as before.
28th September 1925. No change.
29th September 1926. Œdema of sheath decreased but laminitis as before.
30th September-1st October 1925. Ditto.
2nd October 1925. Œdema and laminitis much reduced.
3rd October 1925. Ditto.
5th October 1925. Slight œdema of sheath and laminitis.
11th October 1925. 1,001 lb.
18th October 1925. 1,000 lb.
23rd October 1925. Repeated intravenous injection of "Bayer 205" (50 c.c.).
24th October 1925. Symptoms of laminitis and œdema sheath.
25th October 1925. Acute laminitis and œdema sheath.
26th October 1925. 1,008 lb. Acute laminitis. Great weakness in hind legs.
27th October 1926. Acute laminitis. Walks very stiffly.
28th October-8th November 1925. Ditto.
9th November 1925. Slightly improved. Bed sores on shoulders, hock and elbow-point.
10th November 1925. Ditto. ditto.
11th-17th November 1925. Improving. Bed sores healing.
18th November 1925. Much improved.
22nd November 1925. 908 lb.
29th November 1925. 1,022 lb.
6th December 1925. 1,024 lb.
13th December 1925. 1,056 lb.
20th December 1925. 1,040 lb.
27th December 1925. 1,060 lb.
3rd January 1926. 1,080 lb.
10th January 1926. 1,082 lb.
17th January 1926. 1,088 lb.

Weekly weights in pounds after this date were as follows :—

1020, 1040, 1036, 1040, 1036, 1028, 1028, 1018, 1008, 1008, 980, 1008, 1000, 1010, 1040, 1030, 1028, 1018, 1014, 1024, 1008, 1018, 1024, 1016, 1012, 1004, 1000, 1010, 1014, 1036, 1030, 1038, 1044, 1022, 1044, 1046, 1040, 1024, 1032, 1026, 1028, 1030, 1046, 1032, 1036, 1030.

The animal did not relapse and steadily improved in condition and was discharged on 16th December 1926. (See Phopographs.)

(1) Prophylactic action of tartar emetic ; (ii) Therapeutic action of combined treatment, "Bayer 205" intravenously at 5 grams per 1,000 lb. and tryparsamide intrathecally at 20 c.c. of 0·1 per cent. solution, repeated after a month's interval (successful).

Mare No. 68. (Plates XII and XXIV.)

28th August 1925. 1,120 lb. 5 p.m. Injected intravenously 56 c.c. M/10 tartar emetic solution at the rate of 5 c.c. per 100 lb. body weight.

29th August 1925. Repeated the above injection.
30th August 1925. Ditto.
4th September 1925. Injected 1 c.c. citrated blood from rabbit No. 30A, showing trypanosomes 6 per field.
6th September 1925. 1,130 lb.
12th September 1925. Conjunctival mucous membrane icteric.
16th September 1925. Œdema hind legs.
23rd September 1925. Injected intravenously 56 c.c. of a 10 per cent. solution of "Bayer 205" and 22 c.c. of a 0·1 per cent. solution of tryparsamide intrathecally. (Two punctures had to be made in meninges before injection was accomplished, and fluid withdrawn was slightly blood tinged.) After injection, mare showed unsteady gait, but took her rations well.
24th September 1925. Condition of gait improved.
25th September 1925. Gait improved, but walks cautiously, as if animal does not possess sufficiently reliable control over body. There is no external exhibition of symptoms, such as œdema, but the drug appears to have exercised a general action manifested by lack of sufficient control over body.
26th September 1925. No change.
27th September 1925. 1,008 lb. Gait improved.
28th and 29th September 1925. No change.
30th September 1925. Walks better; no other symptoms.
1st October 1925. Ditto.
3rd October 1925. Walks normally.
11th October 1925. 1,022 lb.
18th October 1925. 1,015 lb.
23rd October 1925. Injected 51 c.c. of a 10 per cent. solution of "Bayer 205" intravenously and 20·4 c.c. of a 0·1 solution of tryparsamide intrathecally (entered with difficulty).
24th October 1925. Shows signs of laminitis.
25th October 1925. Acute laminitis.
26th October 1925. 1,064 lb. Slight laminitis.
27th October 1925. Slight laminitis.
28th October 1925. Ditto.
29th October 1925. Recovered.
22nd November 1925. 1,080 lb.
29th November 1925. 1,080 lb.
6th December 1925. 1,088 lb.
13th December 1925. 1,090 lb.
20th December 1925. 1,090 lb.
27th December 1925. 1,092 lb.
3rd January 1926. 1,086 lb.
10th January 1926. 1,084 lb.
17th January 1926. 1,034 lb.

Weekly weights in pounds after this date were as follows:—
1024, 1028, 1040, 1036, 1012, 1028, 1036, 1060, 1022, 1030, 1050, 1018, 1020, 1024, 1064, 1060, 1070, 1080, 1056, 1087, 1080, 1070, 1087, 1096, 1072, 1064, 1068, 1070, 1090, 1080, 1100, 1096, 1078, 1100, 1106, 1146, 1140, 1178, 1098, 1102, 1092, 1106, 1094, 1120, 1096, 1122, 1120. The animal did not relapse, fed well and was discharged in good condition on 16th December 1926. (See Photographs.)

(i) Prophylactic action tartar emetic; (ii) Therapeutic action combined treatment "Bayer 205" intravenously 5 grams per 1,000 lb. and tryparsamide intrathecally, 20 c.c. of 0·1 per cent. solution per 1,000 lb.; repeated after one month.

Horse No. 70. (Plate XII.)

30th August 1925. 796 lb. 11-0 a.m. Injected intravenously 40 c.c. of M/10 tartar emetic solution, at the rate of 5 c.c. per 100 lb. body weight.

31st August 1925. Repeated injection.
1st September 1925. Repeated injection.
4th September 1925. Injected 1 c.c. citrated blood from rabbit No. 230A, showing trypanosomes 6 per field.

8th September 1925. 812 lb.
9th September 1925. Conjunctival mucous membrane slightly injected.

12th September 1925. Feeds fairly; conjunctival mucous membrane deeply injected and icteric.
23rd September 1925. Injected intravenously 40 c.c. of 10 per cent. solution of " Bayer 205 " and 16 c.c. of 0·1 per cent. solution of tryparsamide intrathecally.
24th September 1925. Fairly distinct urticarial eruptions all over body; œdema sheath, upper lips, angle of jaws, and eyelids.
25th September 1925. Urticarial eruptions disappeared; œdema of eyelids also disappeared, but slight œdema of lips and sheath remains.
26th September 1925. Slight œdema of sheath only remains, but there is evident laminitis.
27th September 1925. 728 lb. No change.
28th September 1925. Same as yesterday.
29th September 1925. Œdema and laminitis decreased.
30th September 1925. No œdema; slight laminitis.
1st October 1925. Ditto.
3rd October 1925. Ditto.
11th October 1925. 823 lb.
18th October 1925. 800 lb.
23rd October 1925. Injected 41 c.c. of 10 per cent. solution of " Bayer 205 " intravenously and 16·4 c.c. of a 0·1 per cent. solution of tryparsamide intrathecally.
24th October 1925. Shows sign of laminitis.
25th October 1925. Acute laminitis, walks with great difficulty, was found lying down when first seen in morning, but later got up, very weak; feeds fairly.
26th October 1925. 861 lb. Acute laminitis, not putting weight on hind legs, very weak, feeds fairly.
27th October 1925. Acute laminitis, very weak.
28th October 1925. Ditto.
29th October 1925. Ditto.
30th October 1925. Symptoms improved; feeds fairly.
31st October 1925. Lying down; feeds fairly.
1st November 1925. Ditto.
2nd November 1925. 11-30 a.m. Withdrew about 20 c.c. cerebro-spinal fluid; centrifuged about 8 c.c. of the fluid; deposit negative for trypanosomes. Stained, also negative. Died during the night.

Therapeutic effect of " Bayer 205 " combined treatment (intravenous at 5 grams per 1,000 lb.; intrathecal at 20 c.c. of 0·1 per cent. solution per 1,000 lb.) repeated after a month's interval.

Horse No. 69. (Plates XIII and XXV.)

4th September 1925. Injected 1 c.c. citrated blood from rabbit No. 230A, showing trypanosomes 6 per field.
8th September 1925. 812 lb.
9th September 1925. Conjunctival mucous membrane injected.
10th September 1925. Feeds fairly.
12th September 1925. Feeds fairly; conjunctival mucous membrane deeply injected and icteric.
16th September 1925. Œdema hind legs.
23rd September 1925. 3 p.m. Injected intravenously 40 c.c. of 10 per cent. solution of " Bayer 205 " and 16 c.c. of a 0·1 solution of " Bayer 205 " intrathecally. 10 minutes after injection there was profuse sweating, which lasted for a few minutes. Symptoms before injection were:—feeds fairly (eats only grass); slight œdema of the upper and lower lips, eyelids, sheath, and hind legs.
26th September 1925. Œdema lips, eyelids, and sheath decreased; symptoms of laminitis rather marked.
27th September 1925. No change; 740 lb.
28th September 1925. Ditto.
29th September 1925. No œdema; laminitis as before.
30th September 1925. Laminitis still present.
1st October 1925. Ditto.
2nd October 1925. Laminitis much reduced.
3rd October 1925. Only slight laminitis remains.
5th October 1925. Ditto.
11th October 1925. 882 lb.
18th October 1925. 880 lb.
23rd October 1925. Injected 44 c.c. of a 10 per cent. solution of " Bayer 205 " intravenously and 17·6 c.c. of a 0·1 per cent. solution of " Bayer 205 " intrathecally.

24th October 1925. Shows symptoms of laminitis, and œdema sheath.
25th October 1925. Acute laminitis and œdema sheath.
26th October 1925. 784 lb. Ditto.
27th October 1925 to 2nd November 1925. Symptoms persisting.
3rd November 1925. Acute laminitis ; walks very stiffly.
4th to 6th November 1925. Ditto.
7th November 1925. Acute laminitis ; walks very stiffly ; bed sores on hips due to falling over.
8th to 10th November 1925. Ditto.
11th November 1925. Improving and bed sores also drying up.
12th to 17th November 1925. Ditto.
18th November 1925. Very slight laminitis.
19th to 23rd November 1925. Ditto. 766 lb. on 22nd November 1925.
24th November 1925. Recovered.
29th November 1925. 772 lb.
6th December 1925. 806 lb.
13th December 1925. 796 lb.
20th December 1925. 796 lb.
27th December 1925. 812 lb.
5th January 1926. 810 lb.
10th January 1926. 812 lb.

Weekly weights in pounds after this date were as follows :—
800, 778, 804, 782, 790, 852, 804, 800, 786, 800, 794, 794, 812, 800, 806, 856, 820, 840, 840, 850, 828, 828, 830, 826, 830, 832, 836, 840, 844, 855, 840, 878, 872, 846, 828, 852, 802, 834, 820, 830, 815, 820, 814, 832, 836, 850, 846, 860, 864. The animal remained well except for symptoms of lameness on both fore legs on 10th September 1926 and of laminitis on 13th September 1926. The latter condition parsisted until 11th November 1926 when it showed slight improvement. It was discharged on 16th December 1926 apparently in good condition (see Photographs), but when about to be sent to the branch laboratory at Bareilly, during the first week of January 1927, it showed distinct symptoms in gait of partial paralysis. Cerebro-spinal fluid (4 c.c.) centrifuged and examined on 17th January 1927, and again on 25th January 1927, was found negative for trypanosomes.

(i) Tolerance to and prophylactic effect of 18 daily intravenous injections of tartar emetic ; (ii) Therapeutic effect of "Bayer 205" combined method—intravenously at 5 grams per 1,000 lb., and intrathecally at 20 c.c. of 0·1 per cent. solution per 1,000 lb.

Horse No. 21A. (Plates XIII and XXV.)

17th July 1925. 910 lb. 2-30 p.m. Injected intravenously 18 c.c. of M/10 solution of tartar emetic, at the rate of 2 c.c. per 100 lb. body weight. There was a slight increase in respiration after the injection.
18th July to 3rd August 1925. Repeated the above injection daily.
7th August 1925. 868 lb.
29th August 1925. 4 p.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 235A "pony surra strain," showing trypanosomes one per two fields.
4th September 1925. Urticaria, belly and thighs, in the form of small swellings, of the size of gram grains.
8th September 1925. 896 lb. Urticaria spread all over body, of same size as before.
12th September 1925. Conjunctival mucous membrane slightly icteric.
13th September 1925. Urticarial swellings decreased.
16th September 1925. Œdema sheath.
21st September 1925. Ditto.
23rd September 1925. Œdema sheath has spread forwards under belly. Injected intravenously 45 c.c. of a 10 per cent. solution of "Bayer 205" and 18 c.c. of a 0·1 per cent. solution intrathecally.
24th September 1925. Feeds fairly ; eats only grass. Œdema of upper and lower lips ; œdema sheath increased.
25th September 1925. Œdema sheath and belly increased ; œdema lips decreased ; muco-purulent discharge from right eye ; feeds fairly (only grass, but no grain).
26th September 1925. Above symptoms appreciably decreased ; feeds better. 3-20 p.m. Lay down and after a few minutes got up again ; dull looking ; then stood quietly.

27th September 1925. 845 lb. Œdema sheath and belly as before ; few well-marked symptoms present.
28th September 1925. Œdema slightly decreased.
29th September 1925. Slight œdema remaining ; feeds well.
30th September and 1st October 1925. Ditto.
5th October 1925. Now normal in appearance.
11th October 1925. 856 lb.
18th October 1925. 845 lb.
23rd October 1925. Injected intravenously 42·5 c.c. of a 1·0 per cent. solution of " Bayer 205 " and 17 c.c. of a 0·1 per cent. solution intrathecally.
24th October 1925. Shows symptoms of laminitis, and œdema of sheath.
26th October 1925. Very slight laminitis and œdema sheath.
27th October 1925. Œdema sheath.
28th and 29th October 1925. Ditto.
30th October 1925. Recovered from above symptoms.
23rd November 1925. 899 lb.
29th November 1925. 908 lb.
6th December 1925. 924 lb.
13th December 1925. 930 lb.
20th December 1925. 922 lb.
27th December 1925. 918 lb.
3rd January 1926. 920 lb.
10th January 1926. 922 lb.
17th January 1926. 900 lb.

Weekly weights in pounds after this date were as follows :—
876, 910, 896, 888, 890, 830, 880, 852, 858, 844, 850, 884, 900, 902, 934, 920, 920, 916, 913, 930, 896, 890, 896, 936, 920, 916, 912, 908, 904, 896, 900, 908, 844, 908, 896, 896, 914, 906, 915, 912, 904, 910, 920, 914, 920, 906, 916, 920. The animal did not relapse, fed well and was discharged in excellent condition on 16th December 1926. (See Photographs.)

(i) Test of tolerance towards repeated large doses of tartar emetic ; (ii) Prophylactic action of tartar emetic ; (iii) Therapeutic action ' Bayer 205 " by combined method, intravenously at 5 grams per 1,000 lb. body weight, and intrathecally at 20 c.c. of a 0·1 per cent. solution per 1,000 lb.—single administration.

Horse No. 35. (Plates XIV and XXV.)

19th July 1925. 784 lb. 3-10 p.m. Injected intravenously 78 c.c. of M/10 tartar emetic at the rate of 10 c.c. per 100 lb. body weight. After injection, respiration increased in rate, with frequent yawning ; showed inclination to lie down, but did not lie, pawing ground ; within a few minutes passed fæces three times, with a tendency to looseness. After half-an-hour, the symptoms gradually disappeared, fæces somewhat sloppy during the night.
20th July 1925. 2-30 p.m. Injected intravenously 78 c.c. M/10 tartar emetic.
21st July 1925. 12 noon. Repeated injection.
22nd July 1925. 12 noon. Repeated injection. After injection, animal was dull and entirely off feed whole day, and showed slight œdema of sheath and under belly.
23rd July 1925. 4 p.m. Inoculated subcutaneously 1 c.c. of citrated blood from rabbit No. 148A, showing trypanosomes one in five fields.
24th July 1925. Œdema appeared also under sternum.
26th July 1925. Œdema under belly, sternum and sheath.
28th July 1925. Œdema disappearing.
13th August 1925. 784 lb.
29th August 1925. Bled 50 c.c. from jugular vein, and injected subcutaneously into dog 31.
8th September 1925. 794 lb.
23rd September 1925. 800 lb.
5th October 1925. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 291, showing trypanosomes 1 per specimen.
11th October 1925. 780 lb.
17th October 1925. Œdema hind legs and sheath.
18th October 1925. 782 lb. Ditto.
19th October 1925. Œdema increasing on sheath.
20th October 1925. Œdema sheath and belly.
21st October 1925. Feeds fairly, dull, and œdema as before.

22nd October 1925. Œdema decreasing.
23rd October 1925. Feeds fairly, dull, œdema decreasing. Injected intravenously 39·1 c.c. of 10 per cent. solution of " Bayer 205 " and 15·6 c.c. of 0·1 per cent. solution of " Bayer 205 " intrathecally.
24th October 1925. Small urticarial eruptions appear over body, especially on neck, shoulders, chest and belly, and also shows symptoms of slight laminitis. Œdema sheath.
25th October 1925. 780 lb. Urticarial eruptions decreased; œdema sheath increasing, laminitis.
26th October 1925. Dull, laminitis, œdema sheath.
27th October 1925. Ditto.
28th October 1925. Ditto.
29th October 1925. Dull, laminitis, œdema sheath.
30th October 1925. Improved.
6th November 1925. 760 lb.
14th November 1925. 750 lb.
22nd November 1925. 770 lb.
29th November 1925. 748 lb.
6th December 1925. 812 lb.
13th December 1925. 816 lb.
20th December 1925. 812 lb.
27th December 1925. 816 lb.
3rd January 1926. 824 lb.

Weekly weights in pounds after this date were as follows: -
826, 816, 768, 796, 776, 782, 784, 784, 812, 784, 764, 766, 766, 768, 800, 802, 804, 800, 788, 794, 778, 812, 776, 770, 778, 780, 796, 796, 800, 818, 800, 800, 812, 818, 800, 810, 802, 812, 804, 800, 796, 810, 800, 804, 815, 820, 804, 818, 816. The animal did not relapse, fed well and was discharged in excellent condition on 16th December 1926. (See Photographs.)

(i) Infected untreated control to Horse No. 28 (prophylactic action " Bayer 205," 10 grams), 22nd September 1925; (ii) Therapeutic effect tryparsamide *in extremis*, nil.

Horse No. 65. (Plate XIV.)

22nd September 1925. 2-15 p.m. Injected subcutaneously 1 c.c. citrated blood from rabbit No. 270, showing trypanosomes 25 per field.
27th September 1925. 570 lb.
29th September 1925. Feeds fairly, weak, lying down, condition bad, teeth exposed with closed jaws.
Injected intravenously 52 c.c. of a 10 per cent. solution of tryparsamide and 12 c.c. of a 0·1 per cent. solution of the same drug intrathecally. Examined cerebro-spinal fluid after centrifugation; trypanosomes found in deposit at the rate of two per field.
2-30 p.m. Animal dying, unconscious.

(i) Test of innocuousness of tryparsamide injected intrathecally at fortnightly interval; (ii) Therapeutic effect " Bayer 205 " intravenously alone at 5 grams per 1,000 lb. administered 5 days after intrathecal infection (successful).

Horse No. 67. (Plates XV and XXV.)

22nd September 1925. 918 lb. 3 p.m. Injected intrathecally 18 c.c. of a 0·1 per cent. solution of tryparsamide, at the rate of 20 c.c. per 1,000 lb. body weight. No symptoms were produced.
23rd September 1925. 900 lb.
7th October 1925. Injected intrathecally 18 c.c. of a 0·1 per cent. solution of tryparsamide. Slight restlessness after injection.
11th October 1925. 963 lb.
26th October 1925. 924 lb.
14th November 1925. Inoculated intrathecally 2 c.c. of citrated blood from guinea-pig 170, showing trypanosomes swarming
15th November 1925. 830 lb.
19th November 1925. Feeds fairly, dull. Injected intravenously 41·5 c.c. of a 10 per cent. solution of " Bayer 205."
20th November 1925. Symptoms as before. Slow in movement.
21st November 1925. Ditto. Ditto.
22nd November 1925. 835 lb. Ditto.

23rd November 1925. Improving, swelling in hind legs.
24th November 1925. Ditto.
25th November 1925. Swelling hind legs up to hocks.
26th November 1925. Ditto.
27th November 1925. Recovered.
29th November 1925. 884 lb.
6th December 1925. 912 lb.
13th December 1925. 904 lb.
20th December 1925. 902 lb.
27th December 1925. 914 lb.
3rd January 1926. 928 lb.

Weekly weights in pounds after this date were as follows :—

928, 884, 928, 884, 902, 920, 880, 895, 896, 910, 868, 880, 878, 870, 874, 892, 900, 912, 972, 950, 938, 938, 940, 998, 950, 958, 960, 965, 955, 940, 950, 952, 964, 950, 950, 960, 956, 942, 952, 930, 934, 938, 940, 940, 940, 952, 942, 924, 946, 948, 956, 858. The animal did not relapse, fed well and was in good condition when discharged on 16th December 1926. (See Photographs.)

(i) Test of innocuousness of "Bayer 205" injected intrathecally at fortnightly interval (22nd September 1925); (ii) Therapeutic effect "Bayer 205" combined method—intravenously at 5 grams per 1,000 lb. and intrathecally at 20 c.c. of 0·1 per cent. solution per 1,000 lb.—10 days after intrathecal infection. (Parallel experiment to that of Horse 67.)

Horse No. 63. (Plate XV.)

22nd September 1925. 812 lb. 3-20 p.m. Injected intrathecally 16 c.c. of a 0·1 per cent. solution of "Bayer 205" (in "normal" saline solution), at the rate of 20 c.c. per 1,000 lb. body weight. No symptoms produced.

7th October 1925. Injected 16 c.c. of a 0·1 per cent. solution of "Bayer 205" intrathecally, No symptoms.
11th October 1925. 676 lb.
26th October 1925. 801 lb.

14th November 1925. Inoculated intrathecally 2 c.c. citrated blood of guinea-pig No. 170 showing trypanosomes swarming (see also Horse 67).
15th November 1925. 800 lb.
20th November 1925. Feeds fairly.
22nd November 1925. 800 lb.

23rd November 1925. Shows dullness and marked weakness of hind quarters in walking; swelling of both hind legs up to hocks, œdema sheath.

24th November 1925. Shows marked depression and weakness; filling of legs and sunken temples. Injected intravenously 40 c.c. of a 10 per cent. solution of "Bayer 205" (about 5 c.c. probably lost due to struggling), and 16 c.c. of a 0·1 per cent. solution intrathecally (again needle became detached after about 5 c.c. had been injected and a little was lost, rest injected easily). Withdrew about 10 c.c. cerebro-spinal fluid, centrifuged; trypasonomes rare in deposit, about 1 per 5 or 10 fields, few red blood cells.

25th November 1925. Shows weakness of hind quarters during movement, swelling hocks, knees and sheath.

26th November 1925. Ditto.
27th November to 2nd December 1925. Edema sheath. 820 lb. on 29th November 1925.
6th December 1925. 812 lb.
13th December 1925. 802 lb.
20th December 1925. 780 lb.
27th December 1925. 798 lb.
3rd January 1926. 816 lb. Blood examination negative until 10th April 1926. Relapsed 11th April 1926,—trypanosomes 4 per field.

The subsequent history of the animal was as follows :—

12th April 1926. Trypanosomes 6 per field; temperature 102° (morning), 102·4° (evening).
13th April 1926. Trypanosomes 10 per field; temperature 101·6° (morning), 100·8° (evening).
14th April 1926. Trypanosomes absent in blood (cerebro-spinal fluid not examined). Died at 2 p.m. after showing severe symptoms of colic.

TESTS OF TOXICITY OF "BAYER 205" BY INTRATHECAL INJECTION.

Foal No. 72.

4th September 1925. 236 lb. 4-40 p.m. Injected intrathecally 1·18 c.c. of a 2 per cent. solution of "Bayer 205."
4-41 p.m. Got up without difficulty; shook.
4-44 p.m. Nibbles bedding, little pruritis.
4-45 p.m. Seems to be more alert than before injection.
4-48 p.m. Little uneasy, as if more responsive to sensory stimuli.
5-24 p.m. Quite lively, and shows no further symptoms.

Foal No. 49.

4th September 1925. 154 lb. 5-50 p.m. Injected intrathecally 3·1 c.c. of a 1 per cent. "Bayer 205" in distilled water.
5-52 p.m. Got up with some difficulty. Had had some difficulty in properly injecting the solution.
5-55 p.m. Swaying a little.
6 p.m. Sways and staggers when made to walk.
6-30 p.m. Swaying a little on being made to walk, but otherwise normal. Subsequently, no symptoms.

Foal No. 56.

4th September 1925. 200 lb. 3-58 p.m. Injected intrathecally 1 c.c. of a 10 per cent. solution of "Bayer 205".
5-20 p.m. Succumbed (chloroformed *in extremis*), after showing violent symptoms of intoxication (*vide* text of paper).

Records of some preliminary experiments on donkeys (Nos. 30, 41, 36), in which infection of cerebro-spinal system was assured by direct introduction of virulent blood intrathecally, and examination of cerebro-spinal fluid on subsequent days. Treatment was administered intrathecally alone in case of Donkey 30 intrathecally and intravenously in case of Donkey 36, and intravenously alone in case of Donkey 41, when infection was established. Single intervention sufficient for cure, but records of Donkey 41 showed that intravenous treatment alone was also sufficient.

Donkey No. 30.

30th September 1925. 140 lb. 4-30 p.m. Injected intrathecally 1·5 c. c. citrated blood swarming with trypanosomes from rabbit. After injection, donkey showed inability to get up, probably due to injury at seat of puncture. 7 p.m. Could stand, but still weak.
1st October 1925. Off feed. One c.c. cerebro-spinal fluid centrifuged; sediment showed trypanosomes at the rate of one per specimen.
2nd October 1925. Off feed dull. 9-30 a.m. One c.c. cerebro-spinal fluid centrifuged; sediment showed 4 trypanosomes per field. 4 p. m. Unable to withdraw cerebro-spinal fluid, but obtained some sanguineous fluid, which showed trypanosomes at the rate of one per 20 fields. Blood negative. After puncture the animal became restless, was lying with fore legs outstretched, probably caused gross injury at seat of puncture.
3rd October 1925. 10 a.m. Off feed, lying down, with frequent convulsive movements of fore limbs. Withdrew small quantity of sanguineous fluid in attempted intrathecal puncture; fluid negative for trypanosomes, both in centrifuged and uncentrifuged condition. Injected intrathecally 2·8 c.c. of a 0·1 per cent. solution of "Bayer 205." Condition bad since last evening, entirely off feed, and lying down. Destroyed by chloroform.

Donkey No. 41. (Plates XVI and XXVI.)

8th October 1925. 148 lb. Inoculated intrathecally with 1 c.c. citrated blood from rabbit No. 243A, showing trypanosomes 8 per field ("Pony" strain).
9th October 1925. Withdrew about 10 c.c. cerebro-spinal fluid, distinctly blood tinged, centrifuged; in deposit, red corpuscles, trypanosomes at the rate of 2 or 3 per field.
10th October 1925. Feeds fairly, dull. Withdrew about 5 c. c. blood tinged fluid from cerebro-spinal canal; trypanosomes at the rate of 3 per field in centrifuged deposit.
11th October 1925. 142 lb. Deposit from cerebro-spinal fluid shows about 3 trypanosomes per field; feeds fairly, dull.
12th October 1925. Withdrew about 4 c.c. blood tinged fluid from cerebro-spinal canal; trypanosomes present in centrifuged deposit at the rate of 4 per field; feeds fairly, dull.
13th October 1925. Ditto. 1 trypanosome per field, feeds fairly, dull. Treated intravenously alone with "Bayer 205" at 5 grams per 1,000 lb. Before injection took about 7 c.c. of cerebro-spinal fluid, very slightly blood tinged; trypanosomes present in centrifuged sediment to the extent of 40 per field; feeds fairly, dull.

14th-17th October 1925. Feeds fairly, dull.
18th October 1925. 140 lb.
21st October 1925. Feeds fairly, dull.
23rd-27th October 1925. Discharge from left nostril.

The animal remained cured and was discharged on 16th December 1926. (See Photograph.)

Donkey No. 36. (Plates XVI and XXVI.)

6th October 1925. 128 lb. Injected intrathecally 1 c.c. citrated blood from rabbit No. 281A ("Pony" strain).
9th October 1925. Withdrew about 7 c.c. of cerebro-spinal fluid, yellowish, turbid, centrifuged; only 3 trypanosomes seen in specimen of deposit, few red cells, and many leucocytes.
10th October 1925. Withdrew about 1 c.c. of cerebro-spinal fluid; only one trypanosome seen in deposit.
11th October 1925. 120 lb. Withdrew about 5 c.c. cerebro-spinal fluid; only 1 trypanosome in 10 fields seen in centrifuged deposit, distinct leucocytosis.
12th October 1925. Withdrew about 1 c.c. yellowish turbid fluid by intrathecal puncture; 1 trypanosome in 5 fields in centrifuged deposit, leucocytosis.
13th October 1925. Feeds fairly, slightly dull; 5 c.c. blood tinged fluid withdrawn by intrathecal puncture, centrifuged deposit shows 5 trypanosomes per field.
14th October 1925. Injected intravenously 6·4 c.c. of a 10 per cent. solution of "Bayer 205" at the rate of 5 grams per 1000 lb. body weight, and 2·56 c.c. of a 0·1 per cent. solution intrathecally at the rate of 20 c.c. per 1000 lb. body weight. Cerebro-spinal fluid withdrawn before injection, about 7 c.c.; about 1 trypanosome per 3 fields found in centrifuged deposit. Feeds fairly, slightly dull.
15th October 1925. Feeds fairly, slightly dull.
16th-17th October 1925. Œdema sheath.
18th-20th October 1925. Œdema decreasing. 120 lb. on 18th October 1925.
21st October 1925. Œdema disappeared.

The animal developed mange on 17th March 1926, and was treated with sulphur ointment, apparently with good results; otherwise, it remained in good condition and was discharged on 16th December 1926. (See Photograph.)

Evaluation of intravenous-intrathecal treatment with "Bayer 205," upon donkeys in the same manner as indicated by the preliminary experiments. Experiment commenced on 14th October 1925 miscarried as large proportion of the donkeys succumbed to injuries following upon intrathecal puncture (see text of paper dealing with this subject).

Donkey No. 35. (Plates XVII and XXVI.)

14th October 1925. 150 lb. Injected intrathecally 1 c.c. citrated blood from rabbit No. 250A, ("Peora" strain) showing 1 trypanosome in 5 fields.
15th October 1925. Feeds fairly, dull.
18th October 1925. 146 lb.
21st October 1925. Feeds fairly, dull. Injected intrathecally 3 c.c. of a 0·1 per cent. solution of "Bayer 205," and intravenously 7·4 c.c. of a 10 per cent. solution. Cerebro-spinal fluid withdrawn readily before injection; centrifuged, deposit shows trypanosomes fairly numerous, about 4 per field.
22nd October 1925. Feeds fairly, dull.
28th October 1925. Weak.

The animal never showed trypanosomes in blood and was discharged in excellent condition on 16th December 1926. (See Photograph.)

Donkey No. 32.

14th October 1925. 152 lb. Inoculated intrathecally 1 c.c. of citrated blood from rabbit No. 250A ("Peora" strain), showing trypanosomes 1 in 5 fields.
15th October 1925. Off feed, lying down; died later during night.

Evaluation of intravenous-intrathecal treatment with "Bayer 205" upon donkeys. The experiment commenced upon the 14th October 1925, which had resulted in large accidental mortality, was repeated on 20th October 1925 using a fresh set of donkeys. Virulent blood was introduced intrathecally, and as symptoms likely to ensue were thought to be very acute, the experimental treatment was performed upon the following day, 21st October 1925. Again, the experiment was largely vitiated on account of the intervention of a large accidental mortality among the donkeys employed, due to injuries

at the seat of puncture. However, results of value were obtained. The control, untreated donkey, No. 28, succumbed to acute surra (25th November 1925); the control (No. 13) treated once intravenously alone remained definitely cured; donkeys 4, 11, and 17 treated by the intravenous-intrathecal method also remained cured. The others (Nos. 19, 31, 22, 20, 3, and 10) furnished no information, on account of early death, due to injuries.

Out of 12 donkeys injected each intrathecally with 1 c. c. citrated blood of guinea-pig No. 153A ("Peora" strain) on 20th October 1925, six had died by 2 p.m. 21st October 1925.

Donkey 28. (Control untreated donkey.) (Plate XVII.)

20th October 1925. 140 lb. Injected 1 c.c. citrated blood of guinea-pig No. 153A ("Peora" strain) intrathecally.
21st October 1925. Feeds fairly, dull, but least dull of those surviving out of the donkeys infected intrathecally at the same time. Left untreated as control.
26th October 1925. Dull.
30th October 1925. Distinctly wasting.
31st October 1925. Slightly dull.
1st November 1925. Ditto.
5th November 1925. Weak in movements.
21st-24th November 1925. Off feed, lying down.
25th November 1925. 100 lb. Destroyed by chloroform, 11-30 a.m.

Donkey No. 13. (Control, treated intravenously alone.) (Plate XVII.)

20th October 1925. 146 lb. Injected intrathecally 1 c. c. citrated blood of guinea-pig No. 153A ("Peora" strain), showing trypanosomes 5 per field.
21st October 1925. Leucocytosis. Feeds fairly, dull. Injected 7·3 c.c. of a 10 per cent. solution of "Bayer 205" intravenously alone, at the rate of 5 grams per 1000 lb. body weight to serve as control.
22nd October 1925. Feeds fairly, dull.
23rd October 1925. Ditto.

The animal remained completely cured, but died of debility on 22nd March 1926. Cerebro-spinal fluid examined at death was negative for trypanosomes. There were extensive lesions of mange over the body.

Donkey No. 4. (Plates XVIII and XXVI.)

20th October 1925. 178 lb. Injected intrathecally 1 c. c. citrated blood of guinea-pig No. 153A. Peora strain, showing trypanosomes 5 per field.
21st October 1925. Feeds fairly, dull; standing but very dull at time of injection. Fluid withdrawn by intrathecal puncture, very blood-tinged; centrifuged, no trypanosomes seen, but large number of red cells and considerable number of large white cells. Injected intrathecally 3·5 c. c. of a 0·1 per cent. solution of "Bayer 205," and intravenously 8·9 c. c. of a 10 per cent. solution of the same drug.

The animal never showed trypanosomes in blood and was discharged in excellent condition on 16th December 1926. (See Photograph.)

Donkey No. 11. (Plates XVIII and XXVI.)

20th October 1925. 168 lb. Injected as above.
21st October 1925. Leucocytosis. Lying down prostrate. Cerebro-spinal fluid on centrifugation shows small number of red cells and enormous number of large cells, mostly mulberry cells. Injected intrathecally 3·36 c. c. of a 0·1 per cent. solution of "Bayer 205" and 8·4 c. c. of a 10 per cent. solution of the same drug intravenously.
22nd October 1925. Off feed, Lying down.
23rd October 1925. Feeds fairly, sitting down.
1st December 1925. Coughs a little.

The animal suffered from mange from 17th April to 15th May 1926 and was treated with sulphur ointment, apparently with good results. Otherwise, it remained well and never showed evidence of trypanosomiasis. It was discharged on 16th December 1926. (See Photograph.)

Donkey No. 17. (Plates XIX and XXVI.)

20th October 1925. 188 lb. Inoculated intrathecally with 1 c. c. citrated blood of guinea-pig No. 153A, showing trypanosomes 5 per field ("Peora" strain).

21st October 1925. Feeds fairly, dull. Withdrew about 2 c. c. of cerebro-spinal fluid ; deposit contains small number of red cells, and extraordinarily large number of mulberry cells. Injected 3·9 c. c. of a 9·1 per cent. solution of " Bayer 205 " intrathecally and 9·4 c. c. of a 10 per cent. solution of the same drug intravenously. Very dull at time of injection, but able to remain standing.

22nd October 1925. Feeds fairly, dull.

The animal made complete recovery and was discharged in excellent condition on 16th December 1926. (See Photograph.)

Donkey No. 19.

20th October 1925. Inoculated intrathecally 1 c. c. of citrated blood from guinea-pig No. 153A (" Peora " strain), showing trypanosomes 5 per field. Lying down prostrate and motionless at time of injection.

21st October 1925. Off feed, lying down. Cerebro-spinal fluid, centrifuged, contained large number of red cells and some white cells. Injected 3 c. c. of a 0·1 per cent. solution of " Bayer 205 " intrathecally and 7·3 c. c. of a 10 per cent. solution of the same drug intravenously.

22nd October 1925. Off feed, lying down.

23rd October 1925. Ditto.

24th October 1925. Ditto.

25th October 1925. Died during the night.

Donkey No. 31.

20th October 1925. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 153A (" Peora " strain), showing trypanosomes 5 per field.

21st October 1925. Off feed, lying down. Died at 10 a.m.

Donkey No. 22.

20th October 1925. Injected with trypanosomes as above. Died during the night.

Donkey No. 20.

20th October 1925. Injected with trypanosomes as above. Died during the night.

Donkey No. 3.

20th October 1925. Injected with trypanosomes as above.

21st October 1925. Leucocytosis. Off feed, lying down. Died at 2 p.m.

Donkey No. 10.

20th October 1925. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 153A (" Peora " strain), showing trypanosomes 5 per field. Died during the night.

Experiment to determine by direct method the value of the combined intravenous-intrathecal treatment with " Bayer 205."

Twelve ponies, specially procured, infected at the same time by intrathecal injection of highly virulent blood.

(i) Three kept as untreated controls (Nos. 81, 82, 83). No. 81 died apparently on account of injuries received during abortion ; others died of hyperacute trypanosome infection.

(ii) Ponies 74 and 76, treated with " Bayer 205 " intravenously alone, repeated after a month's interval, at 2·5 grams per 1,000 lb., *relapse.*

(iii) Ponies 79 and 80 treated likewise intravenously alone, at 5 grams per 1,000 lb., *cured.*

(iv) Ponies 77, 78, and 86 treated intravenously twice also at 2·5 grams per 1,000 lb. and intrathecally, fortnightly, at same time, *cured.*

(v) Ponies 84 and 85 treated intravenously twice at same intervals at 5 grams per 1,000 lb. and intrathecally, fortnightly, at same time ; pony 84 cured ; pony 85 died early during observations of intercurrent affection (pleuro-pneumonia).

This experiment was set as indicated above after a consideration of the preliminary information furnished by the donkey experiments.

Pony No. 74. (Plate XIX.)

27th November 1925. 328 lb. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.

4th December 1925. 340 lb.

5th December 1925. Injected intravenously 8·2 c. c. of a 10 per cent. solution of " Bayer 205 " at the rate of 2·5 grams per 1000 lb. body weight.

11th December 1925. 358 lb.
18th December 1925. 364 lb. One microfilaria in smears.
25th December 1925. 370 lb.
1st January 1926. 360 lb.
4th Janury 1926. Repeated intravenous injection with " Bayer 205 " (8·2 c.c.).
9th January 1926. 358 lb.
16th January 1926. 364 lb.
14th March 1926. Foal born.
16th March 1926. Relapsed, trypanosomes 1 in 10 fields.
17th March 1926. Trypanosomes 2 per field ; temperature 99° (morning), 100° (evening).
18th March 1926. Trypanosomes 10 per field ; temperature 99·6° (morning), 101° (evening).
19th March 1926. Trypanosomes 10 per field ; temperature 102° (morning), 100·6° (evening).
20th March 1926. 308 lb. Trypanosomes 14 per field ; temperature 100° (morning), 102 (evening).
21st March 926. Trypanosomes 10 per field ; temperature 101·2° (morning), 100·6° (evening).
22nd March 1926. Trypanosomes 2 per field ; temperature 98° (morning), 101° (evening).
23rd March 1926. Trypanosomes 1 per field ; temperature 99·4° (morning), 100·4° (evening).
24th March 1926 Trypanosomes 4 per field ; temperature 98·6° (morning), 100·6° (evening).
25th March 1926. Trypanosomes not discoverable ; temperature 99·4° (morning), 100·2° (evening).
26th March 1926. Trypanosomes not discoverable ; temperature 98·4° (morning), 100° (evening). Weak.
27th March 1926. 304 lb. Trypanosomes 1 in 10 fields ; temperature 100·4° (morning), 101·6° (evening). Feeds fairly.
28th March 1926. Trypanosomes 6 per field ; temperature 100° (morning), 100·8° (evening). Feeds fairly.
29th March 1926. Trypanosomes 24 per field ; temperature 100·8° (morning), 101·8° (evening). Feeds fairly.
30th March 1926. Trypanosomes 40 per field ; temperature 97·8° (morning), 97·2° (evening), Feeds fairly. Injected 15·2 c.c. of a 10 per cent. solution of " Bayer 205 " intravenously, at the rate of 5 grams per 1,000 lb. body weight.
31st March 1926. Trypanosomes not discoverable ; temperature 96·6° (morning), 96° (evening) Very weak, unable to walk. Died during the night.

Pony No. 76. (Plate XX.)

27th November 1925 298 lb. Injected intrathecally 1 c. c. of citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.

4th December 1925. 280 lb.
5th December 1925. Injected 7·4 c. c. of a 10 per cent. solution of " Bayer 205 " intravenously alone, at the rate of 2·5 grams per 1,000 lb. body weight.
7th December 1925. Leucocytosis observable on blood examination.
11th December 1925. 298 lb.
18th December 1925. 296 lb.
25th December 1925. 290 lb.
1st January 1926. 300 lb.
4th January 1926. Repeated intravenous injection with " Bayer 205."
9th January 1926. 294 lb.
16th January 1926. 300 lb.

15th February 1926. Relapsed.

4th March 1926. Injected intravenously 14·4 c.c. of a 10 per cent. solution of " Bayer 205 ", at the rate of 5 grams per 1,000 lb. body weight and 5·76 c.c. of a 0·1 per cent. solution of the same drug intrathecally. The subsequent history of the animal was briefly as follows —

5th March to 26th April 1926. Blood negative for trypanosomes.

27th April 1926. Relapsed.

28th April to 12th August 1926. Blood positive for trypanosomes on most of the days, their number generally not exceeding 10 per field. The animal, however, fed well except during the last week prior to death.

18th July 1926. 270 lb.
30th July 1926. Injected 5·76 c.c of a 0·1 per cent. solution of " Bayer 205 " intrathecally, Centrifuged cerebro-spinal fluid showed trypanosomes 5 per field.
31st July 1926. Injected 5 c.c. of a 10 per cent. solution of " Bayer 205 " intravenously, at the rate of 5 grams per 1,000 lb. body weight.
5th August 1926. Œdema on belly and urticaria.
9th August 1926. Muco-purulent discharge from nostrils.
12th August 1926. Off feed ; lying down. Died during the night.

Pony No. 79. (Plates XX and XXV.)

27th November 1925. 460 lb. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 202A, showing trypanosomes 12 per field. Aborted about 3 p.m.
3rd December 1925. Œdema under chest.
4th December 1925. 420 lb. Ditto.
5th December 1925. Injected 23 c. c. of a 10 per cent. solution of " Bayer 205 " intravenously alone, at the rate of 5 grams per 1000 lb. body weight.
6th December 1925. Feeds fairly ; œdema chest, slight swelling hind legs.
7th December 1925. Feeds fairly ; œdema chest, swelling hind legs decreasing.
8th-10th December 1925. Œdema chest.
11th December 1925 440 lb. Ditto.
12th December 1926. Ditto.
18th December 1925. 464 lb.
25th December 1925. 460 lb.
1st January 1926. 448 lb.
4th January 1926. Repeated intravenous injection (23 c. c.) of " Bayer 205."
9th January 1926. 440 lb.
16th January 1926. 435 lb.
Weekly weights in pounds after this date were as follows :—
440, 452, 446, 442, 448, 450, 456, 445, 440, 434, 436, 440, 452, 440, 448, 450, 472, 440, 450, 482, 468, 470, 475, 483, 484, 484, 488, 496, 508, 504, 510, 504, 496, 490, 484, 484, 490, 484, 480, 475, 485, 500, 496, 490, 504, 524, 509, 508. The animal did not relapse, fed well and was discharged in excellent condition on 16th December 1926.

Pony No. 80. (Plates XX and XXV.)

27th November 1925. 360 lb. Injected intrathecally 1 c.c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.
30th November 1925. Feeds fairly.
4th December 1925. 340 lb.
5th December 1925. Injected 18 c. c. of a 10 per cent. solution of " Bayer 205 " intravenously alone, at the rate of 5 grams per 1000 lb. body weight.
8th December 1925. Dull, lying down in the morning, stood up with some support, but again lay down in sitting position for about half an hour.
9th and 10th December 1925. Feeds fairly, dull.
11th December 1925. 348 lb. Ditto.
18th December 1925. 356 lb.
25th December 1925. 360 lb.
1st January 1926. 370 lb.
4th January 1926. Repeated intravenous injection with " Bayer 205."
9th January 1926. 365 lb.
16th January 1926. 370 lb.
Weekly weights in pounds after this date were as follows :—
380, 370, 364, 362, 360, 380, 375, 320, 324, 328, 316, 320, 324, 325, 330, 326, 330, 318, 328, 342, 348, 350, 356, 344, 348, 348, 340, 350, 364, 358, 358, 352, 356, 358, 358, 360, 366, 360, 368, 365, 360, 348, 356, 264, 354, 370, 378. A dead foal was born on 13th February 1926. The animal did not relapse, fed well and was discharged in good condition on 16th December 1926. (See Photograph.)

Pony No. 77. (Plates XXI and XXVI.)

27th November 1925. 350 lb. Injected intrathecally 1 c.c. of citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.
4th December 1925. 328 lb.
5th December 1925. Injected 8·7 c. c. of a 10 per cent. solution of "Bayer 205 " intravenously at the rate of 2·5 grams per 1,000 lb. body weight and 7 c. c. of a 0·1 per cent. solution of the same drug intrathecally, at the rate of 20 c. c. per 1,000 lb. body weight.

6th-9th December 1925. Feeds fairly.
11th December 1925. 340 lb.
18th December 1925. 346 lb.
21st December 1925. Repeated intrathecal injection with " Bayer 205 " as above.
25th December 1925. 343 lb.
1st January 1926. 344 lb.
4th January 1926. Repeated intravenous and intrathecal injections as on 5th December 1925.
9th January 1926. 336 lb.
16th January 1926. 340 lb.

Weekly weights in pounds after this date were as follows :—
338, 340, 360, 350, 355, 366, 368, 352, 336, 344, 340. 335, 390, 392, 388, 390, 384, 380, 390, 400, 398, 390, 380, 416, 412, 420, 416, 424, 436, 440, 440, 435, 430, 432, 438, 438, 442, 436, 440, 443, 448, 436, 434, 422, 442, 442, 440, 446. The animal did not relapse, fed well and was discharged in good condition on 16th December 1926. (See Photograph.)

Pony No. 78. (Plates XXI and XXVI.)

27th November 1925. 320 lb. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.
4th December 1925. 300 lb.
5th December 1925. Injected 8 c. c. of a 10 per cent. solution of " Bayer 205 " intravenously, at the rate of 2·5 grams per 1,000 lb. body weight and 6·4 c. c. of a 0·1 per cent. solution of the same drug intrathecally, at the rate of 20 c. c. per 1,000 lb. body weight.
11th December 1925. 325 lb.
18th December 1925. 332 lb.
21st December 1925. Repeated intrathecal injection with " Bayer 205."
25th December 1925. 328 lb.
1st January 1926. 325 lb.
4th January 1926. Repeated intravenous and intrathecal injections with " Bayer 205."
9th January 1926. 336 lb.
16th January 1926. 338 lb.

Weekly weights in pounds after this date were as follows :—
340, 345, 352, 342, 345, 355, 350, 336, 356, 368, 356, 360, 402, 400, 390, 395, 408, 392, 400, 406, 408, 412, 408, 414, 404, 412, 414, 416, 428, 436, 430, 428, 420, 430, 430, 430, 432, 436, 440, 440, 444, 454, 440, 430, 446, 455, 450, 454. The animal did not relapse, fed well and was in excellent condition when discharged on 16th December 1926. (See Photograph.)

Pony No. 86. (Plates XXI and XXVI.)

27th November 1925. 356 lb. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.
4th December 1925. 336 lb.
5th December 1925. Feeds fairly. Injected 8·9 c. c. of a 10 per cent. solution of " Bayer 205 " intravenously, at the rate of 2·5 grams per 1,000 lb. body weight and 7·1 c. c. of a 0·1 per cent. solution of the same drug intrathecally (quite successfully).
6th December 1925. Feeds fairly.
7th December 1925. Feeds fairly, dull, aborted during the night.
8th December 1925. Feeds fairly, dull.
9th December 1925. Feeds fairly.
11th-12th December 1925. Feeds fairly.
21st December 1925. Repeated intrathecal injection with " Bayer 205."
22nd-24th December 1925. Feeds fairly.
1st January 1926. 334 lb.
4th January 1926. Repeated intravenous and intrathecal injections with " Bayer 205."
9th January 1926. 336 lb.
16th January 1926. 340 lb.

Weekly weights in pounds after this date were as follows :—
342, 338, 336, 330, 328, 340, 335, 334, 336, 346, 336, 340, 452, 360, 356, 356, 376, 366, 364, 368, 372, 370, 365, 370, 368, 348, 350, 358, 340, 350, 348, 360, 364, 358, 360, 360, 358, 356, 360, 352, 358, 368, 352, 372, 364, 366, 380, 386. The animal did not relapse, fed well and was discharged in excellent condition on 16th December 1926. (See Photograph.)

Pony No. 84. (Plates XXII and XXVI.)

27th November 1925. 245 lb. Injected intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.

2nd December 1925. Weak in movements.
4th December 1925. 244 lb. Weak in movements and slightly dull.
5th December 1925. Injected 12·2 c. c. of a 10 per cent. solution of " Bayer 205 " intravenously, at the rate of 5 grams per 1,000 lb. body weight and 4·9 c. c. of a 0·1 per cent. solution of the same drug intrathecally (quite successfully), at the rate of 20 c. c. per 1,000 lb. body weight.
11th December 1925. 255 lb.
18th December 1925. 264 lb.
21st December 1925. Repeated intrathecal injection with " Bayer 205."
25th December 1925. 270 lb.
1st January 1926. 265 lb.
4th January 1926. Repeated intravenous and intrathecal injections with " Bayer 205."
9th January 1926. 253 lb.
16th January 1926. 258 lb.

Weekly weights in pounds after this date were as follows :—
264, 275, 270, 260, 255, 266, 252, 248, 244, 252, 246, 250, 286, 290, 280, 285, 292, 294, 290, 290, 288, 290, 286, 300, 304, 312, 316, 314, 320, 316, 320, 320, 300, 314, 324, 324, 328, 320, 328, 330, 336, 334, 330, 326, 320, 324, 332, 330. The animal did not relapse, fed well and was discharged in excellent condition on 6th December 1926. (See Photograph.)

Pony No. 85. (Plate XXII.)
27th November 1925. 296 lb. Inoculated intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field. Had aborted a fœtus at 9-30 a.m. ; very weak.
3rd December 1925. Weak in movements ; slight swelling right hock.
5th December 1925. Feeds fairly. Injected 14·9 c. c. of 10 per cent. solution of " Bayer 205 " intravenously, at the rate of 5 grams per 1,000 lb. body weight, and 5·9 c. c. of 0·1 per cent. solution intrathecally, at the rate of 20 c. c. per 1,000 lb. body weight.
6th December 1925. Feeds fairly.
7th December 1925. Very weak in hind quarters.
8th December 1925. Feeds slowly, dull, very weak in hind quarters.
9th December 1925. Ditto.
10th December 1925. Ditto, condition very poor.
11th December 1925. Ditto ; blood examination shows distinct leucocytosis.
12th-18th December 1925. Feeds fairly, very weak in hind quarters.
19th December 1925. Feeds fairly, lying down, very weak.
20th December 1925. Feeds fairly.
21st December 1925. Feeds fairly. Repeated intrathecal injection of " Bayer 205."
27th December 1925 to 3rd January 1926. Feeds fairly.
4th January 1926. Feeds fairly. Injected 14·8 c. c. of a 10 per cent. solution intravenously and 5·9 c. c. of 0·1 per cent. solution intrathecally.
5th January 1926. Sitting down, feeds fairly.
6th-10th January 1926. Lying down, feeds. fairly.
11th January 1926. Shows signs of difficult breathing, died at 9-55 a.m. (*Post-mortem* examination showed advanced pleuro-pneumonia to be the cause of death.)

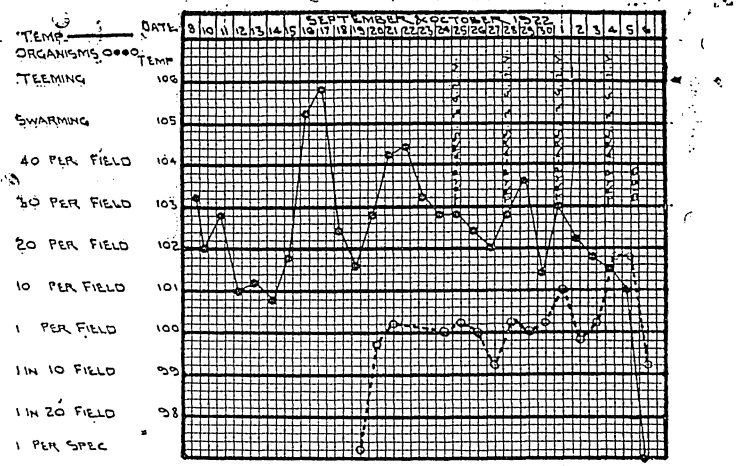
Pony No. 81.
27th November 1925. 272 lb. Inoculated intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field. Had aborted fœtus and lacerated anus and vulva ; very weak. Showed restlessness after injection, lay down. Symptoms of paraplegia. Died during the night.

Pony No. 83. (Plate XXIII.)
27th November 1925. 252 lb. Inoculated intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field.
4th December 1925. Slightly dull. Died during the night.

Pony No. 82. (Plate XXIII.)
27th November 1925. 368 lb. Inoculated intrathecally 1 c. c. citrated blood from guinea-pig No. 202A (" Peora " strain), showing trypanosomes 12 per field. Showed some restlessness after injection.
29th November 1925. Off feed, lying down.
30th November 1925. Feeds slowly.
2nd December 1925. Very marked leucocytosis, feeds slowly.
3rd-6th December 1925. Feeds slowly. Died during the night of 6th December 1925.

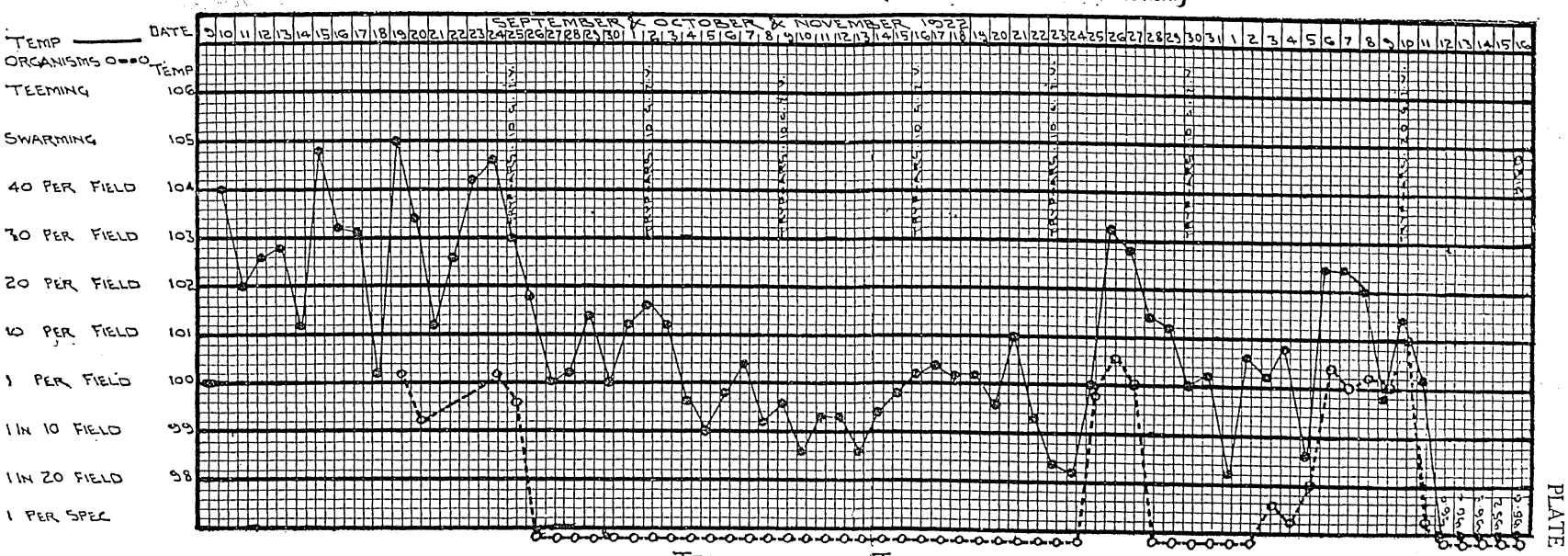
MGIPC—M—IV-2-54—5-3-28—600.

PONY... Nº 174. (NATURALLY CONTRACTED INFECTION.)



TREATMENT - WITH TRYPARSAMIDE.

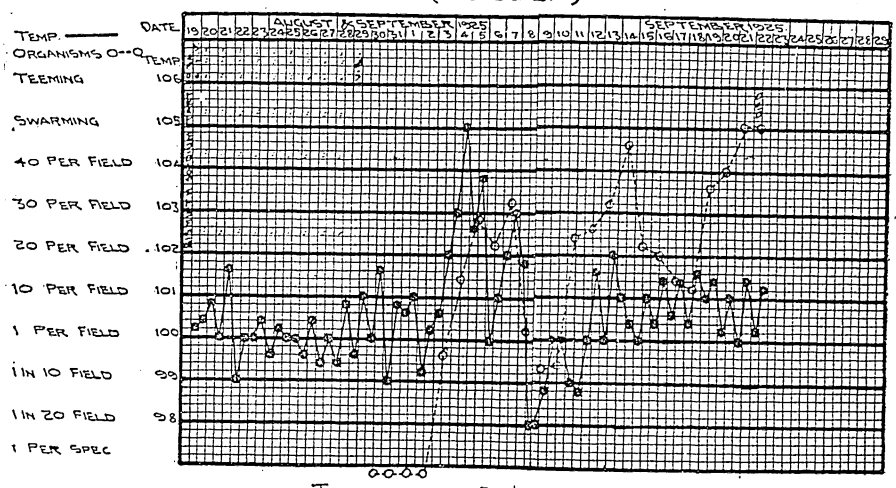
EKKA PONY MARE (NATURALLY CONTRACTED INFECTION.)



TREATMENT WITH TRYPARSAMIDE.

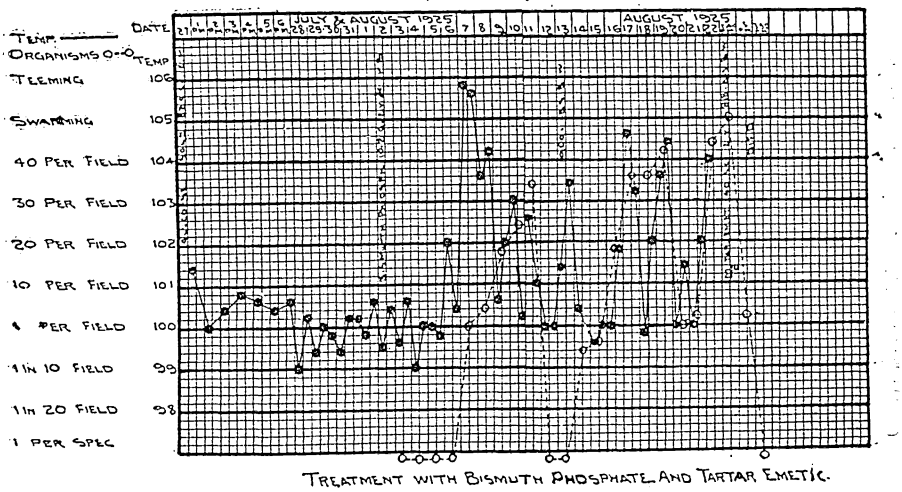
PLATE I.

HORSE Nº 61. (856 LBS. B.W.)



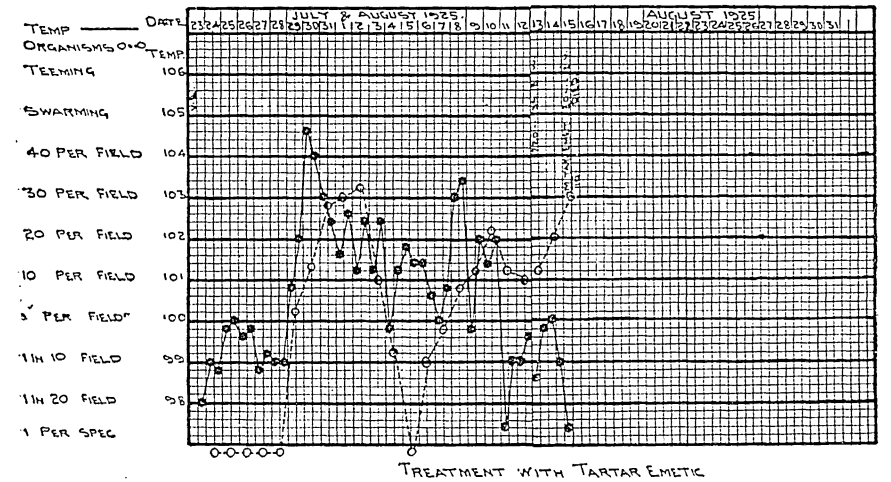
TREATMENT WITH BISMUTH SODIUM TARTRATE.

HORSE Nº 58. (822 LBS. B.W.)



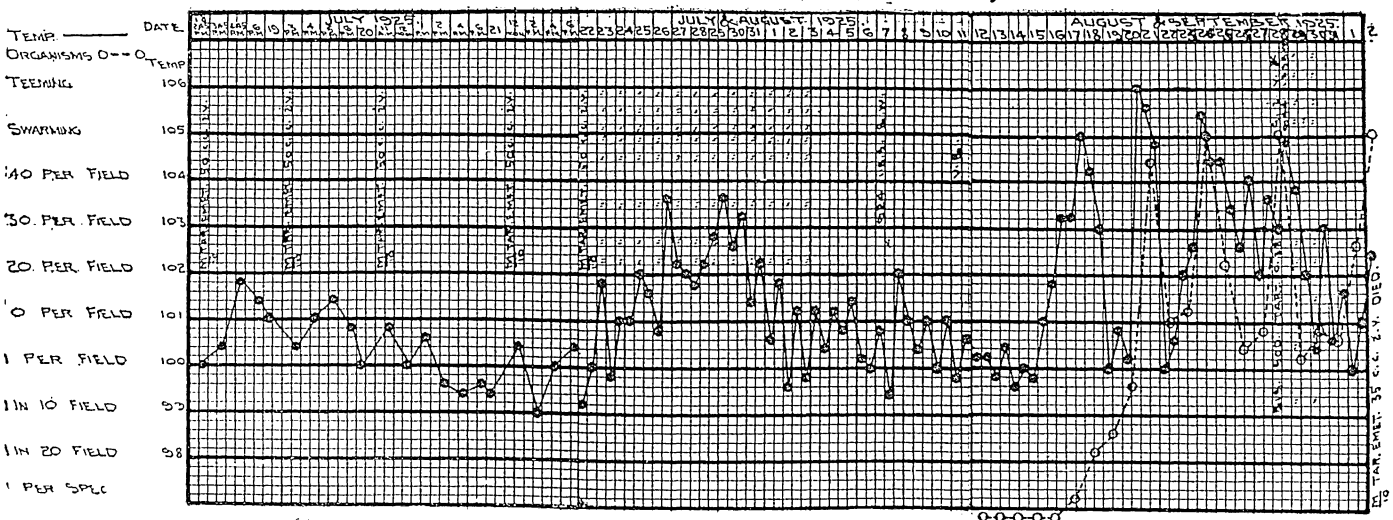
TREATMENT WITH BISMUTH PHOSPHATE AND TARTAR EMETIC.

HORSE Nº 47 (436 LBS. B.W.)



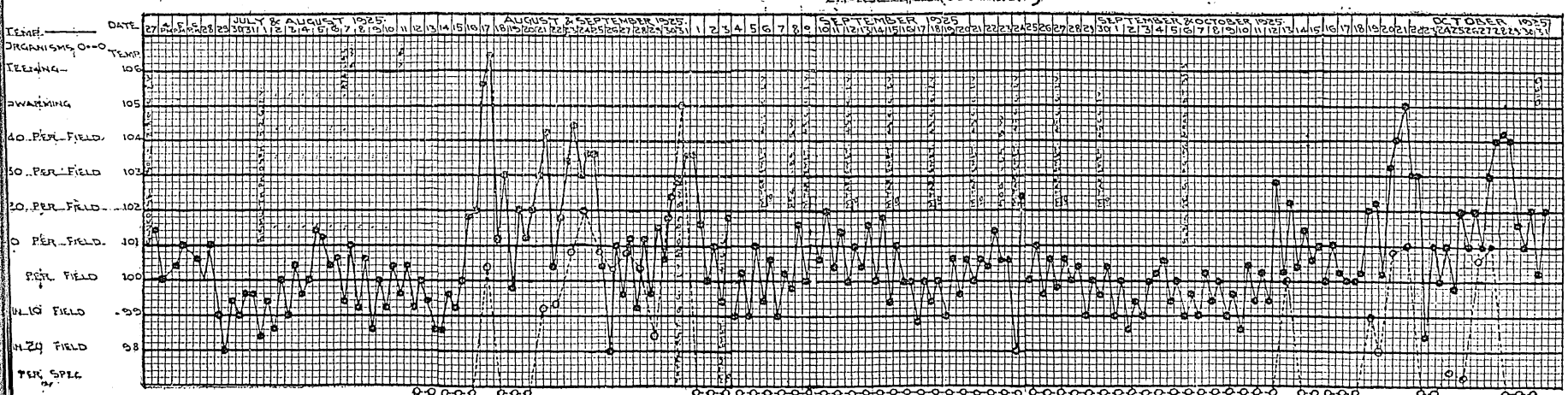
TREATMENT WITH TARTAR EMETIC

HORSE №23 (B.B.A. Lab. B.W.)



TREATMENT WITH TARTAR EMETIC, BISMUTH SODIUM TARTRATE

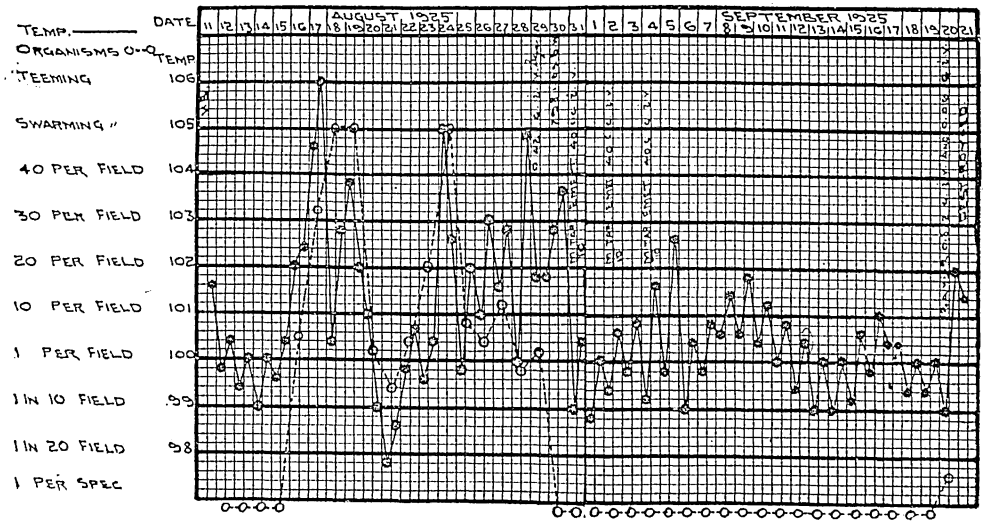
HORSE №48 (B.G.B. Lab. B.W.)



TREATMENT WITH TRYPARSAMIDE AND TARTAR EMETIC

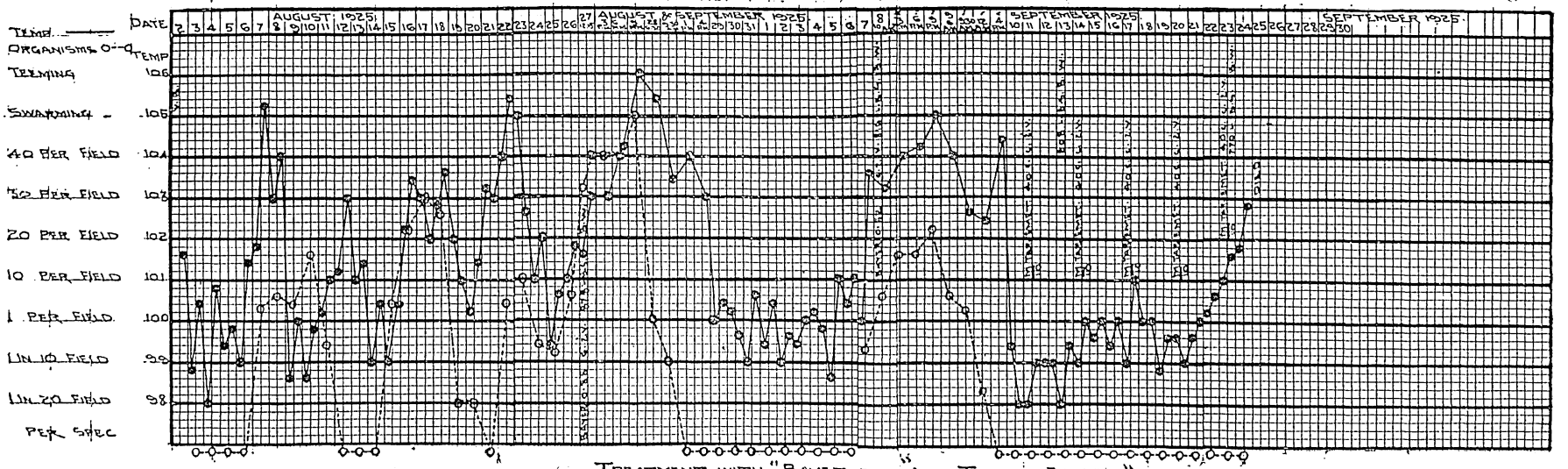
PLATE III.

HORSE No. 54. (846 lbs. B.W.)



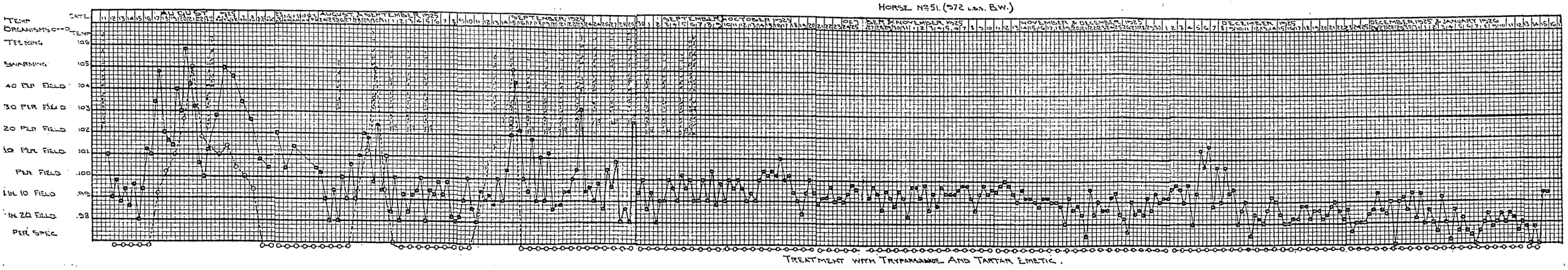
TREATMENT WITH TARTAR EMETIC AND BAYER 205.

HORSE No. 53. (868 lbs. B.W.)

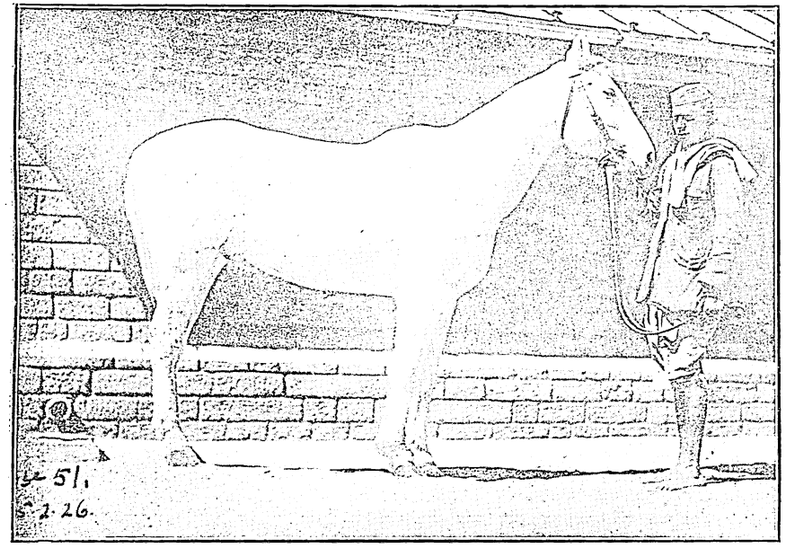


TREATMENT WITH "BAYER 205" AND TARTAR EMETIC"

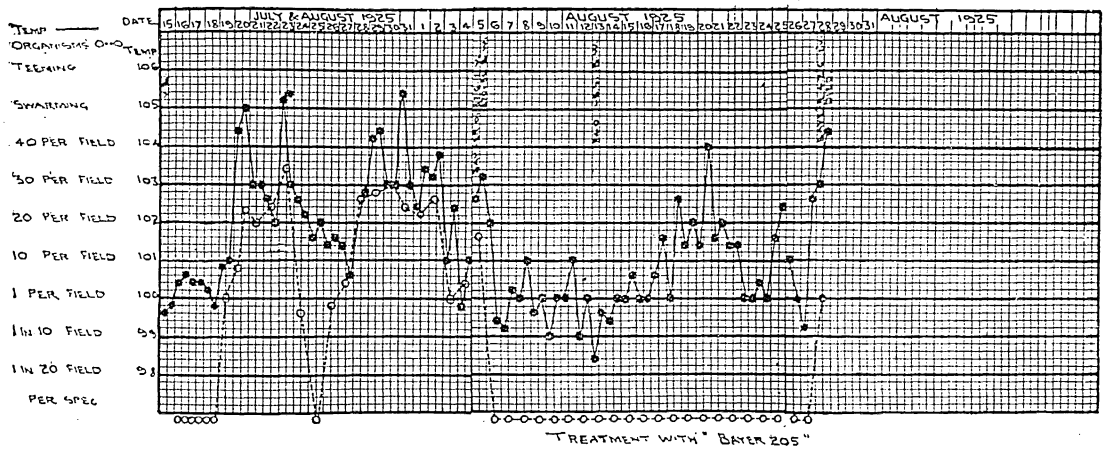
HORSE No 51. (372 Lbs. B.W.)



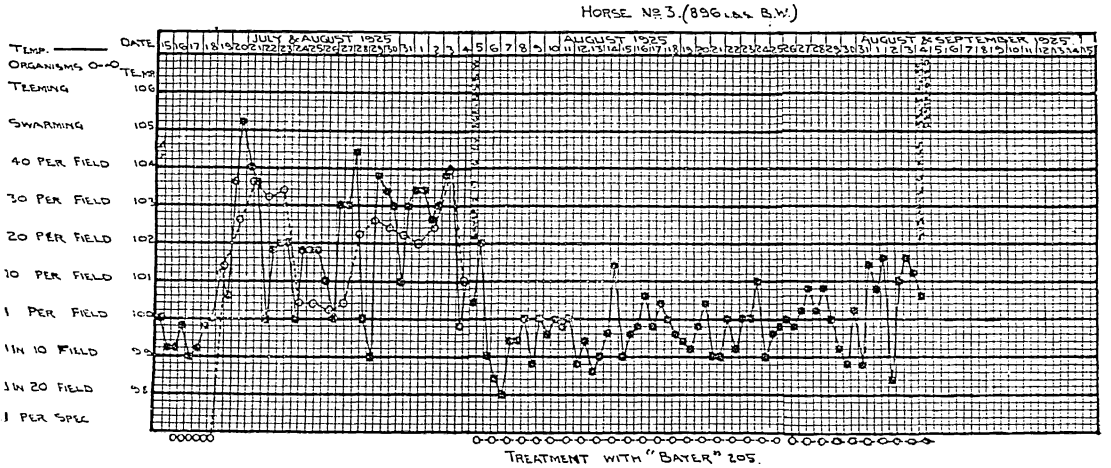
TREATMENT WITH TRYPARSAMIDE AND TARTAR EMETIC.



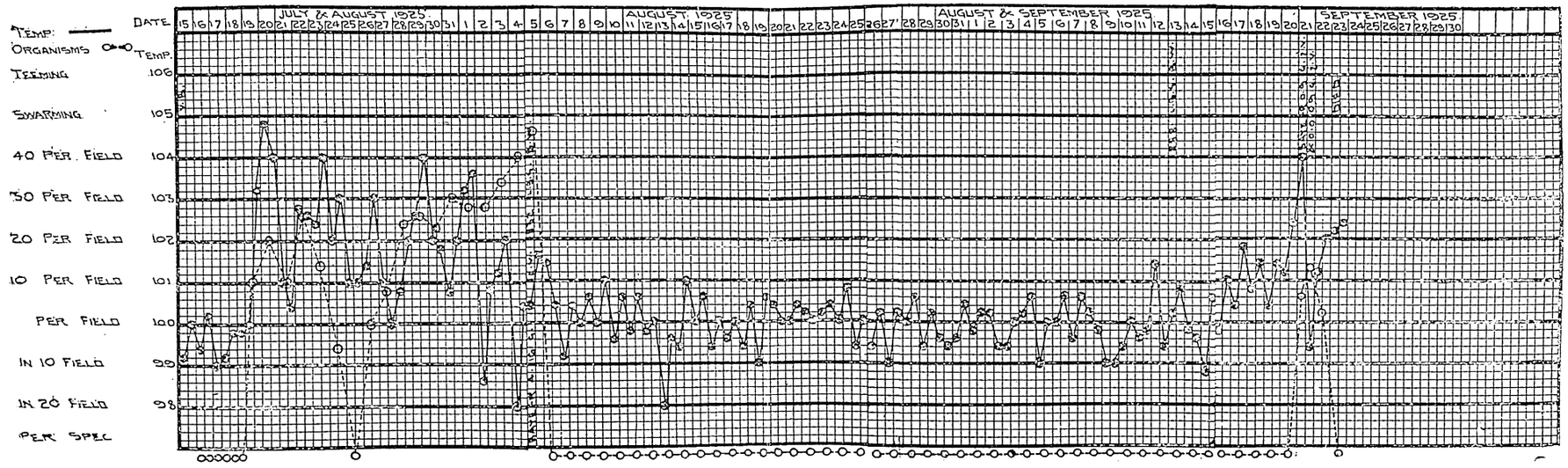
HORSE No 19. (924 lbs. B.W.)



HORSE No 3. (896 lbs. B.W.)

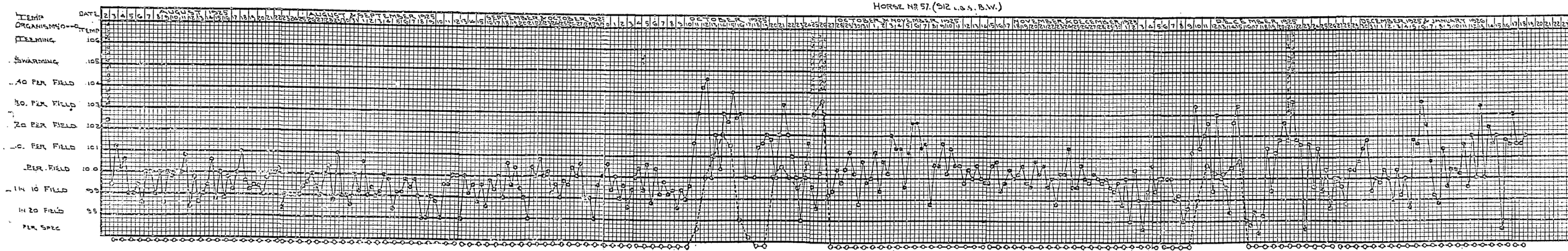


MARE No 2. (906 LBS. B.W.)



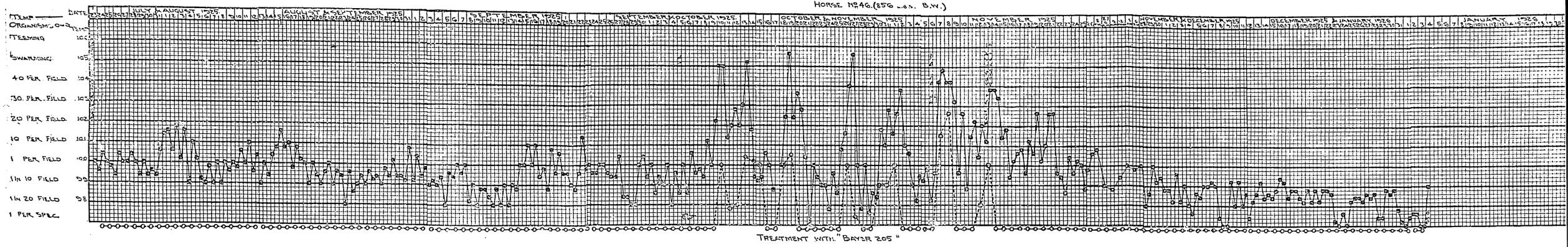
TREATMENT WITH "BAYER 205"

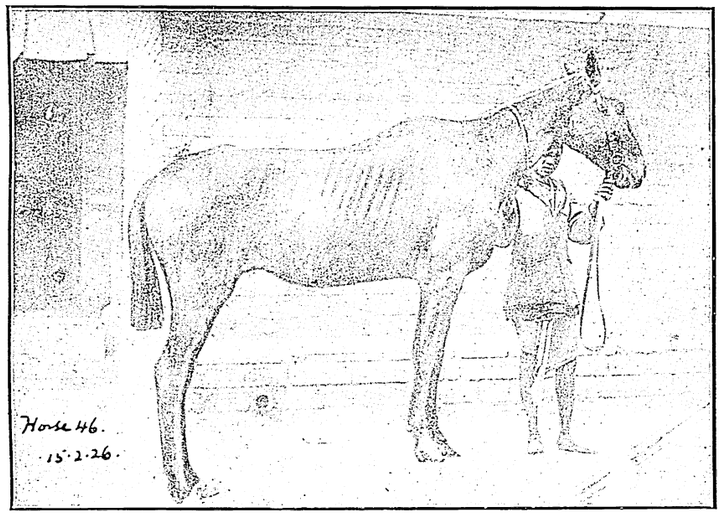
HORSE No 57. (912 LBS. B.W.)



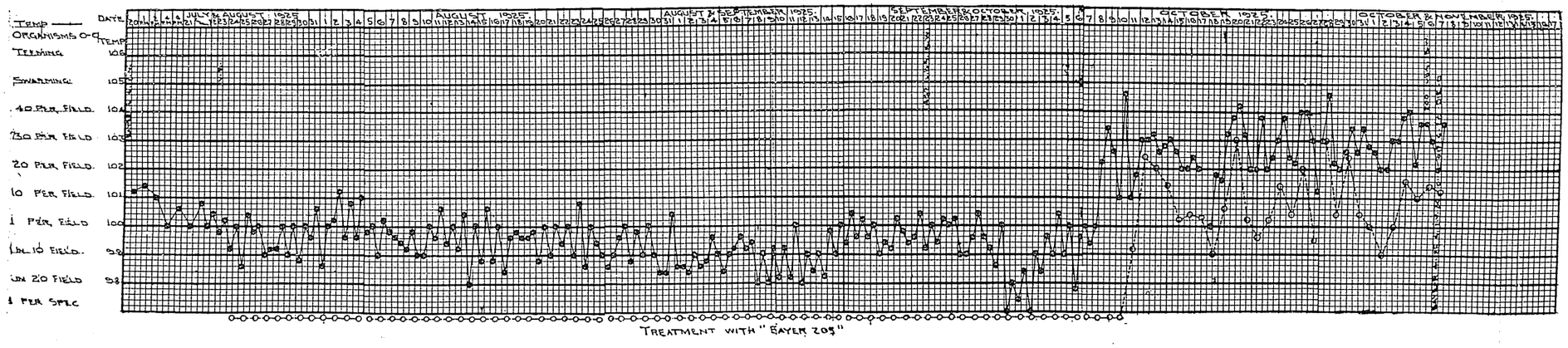
TREATMENT WITH "BAYER 205"

HORSE No 46. (856 LBS. B.W.)

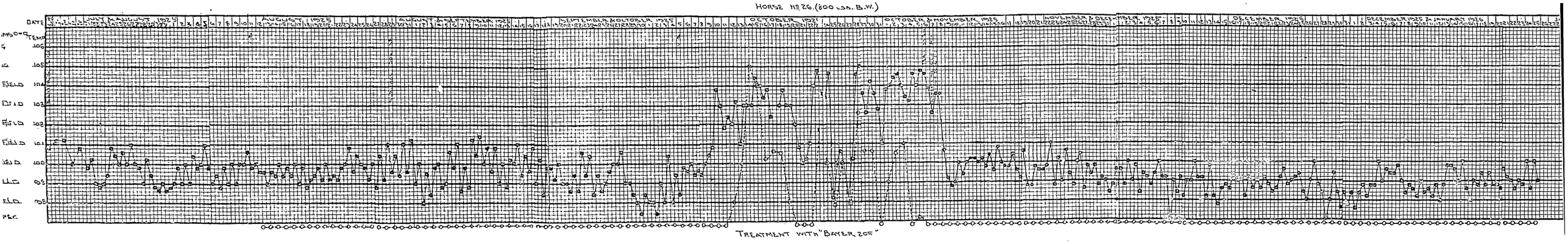


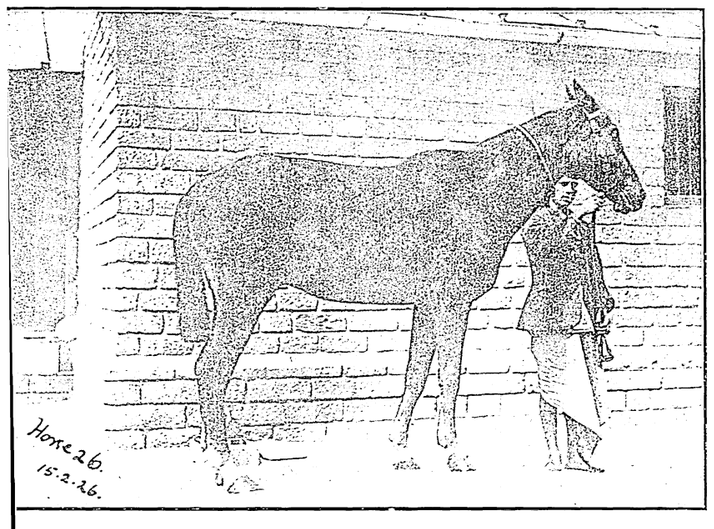


HORSE No. 21B (880 LBS. B.W.)



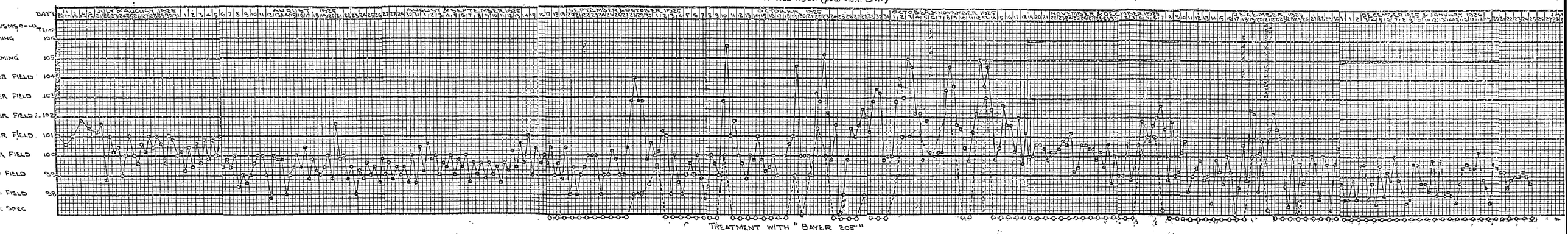
HORSE No 26. (800 LBS. B.W.)

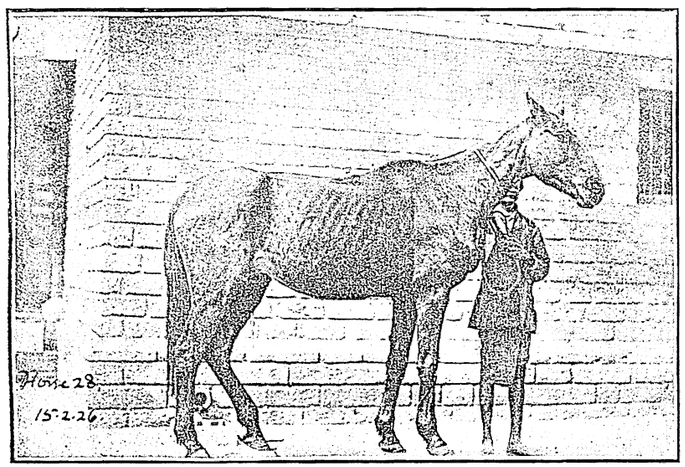




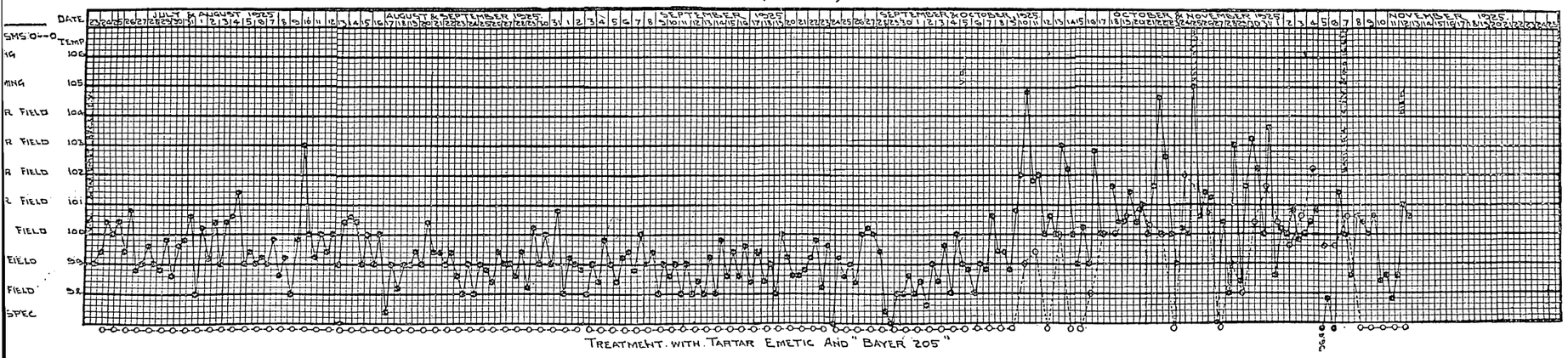
Horse 26.
15.2.26.

HORSE Nº28 (756 LBS. B.W.)

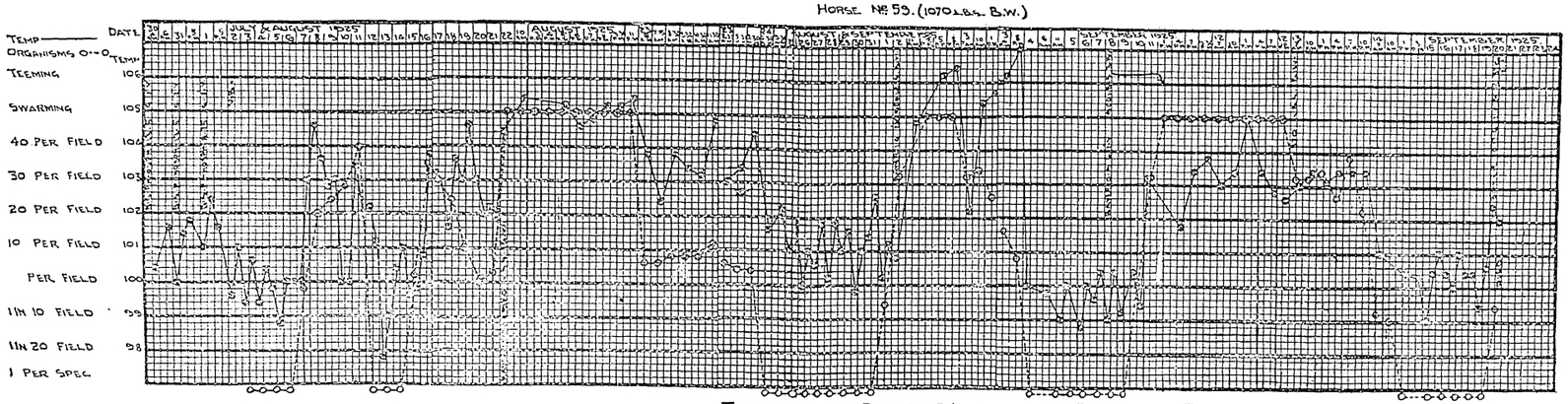




HORSE Nº 45 (878 LBS. B.W.)

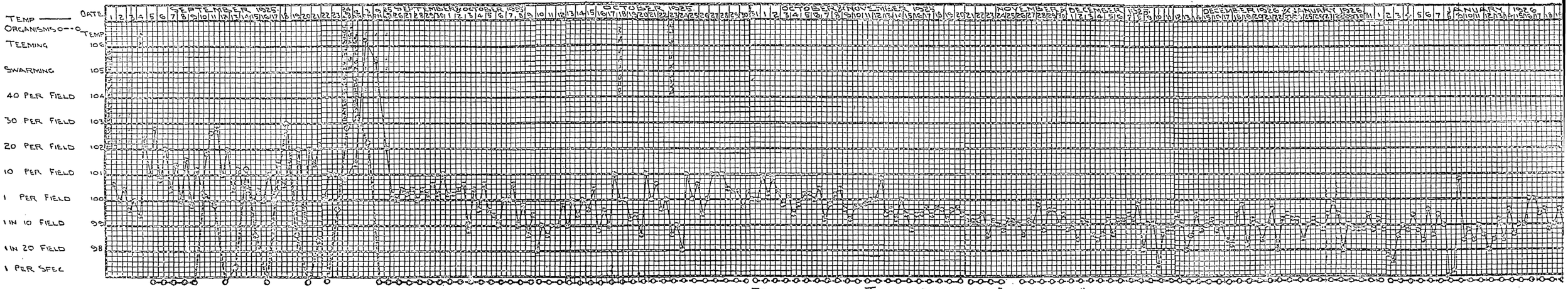


HORSE № 59. (1070 LBS. B.W.)

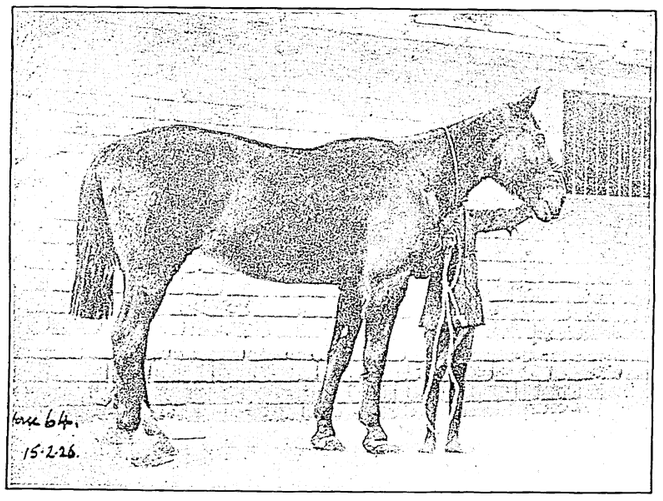


TREATMENT WITH BISMUTH PHOSPHATE AND "BAYER 205"

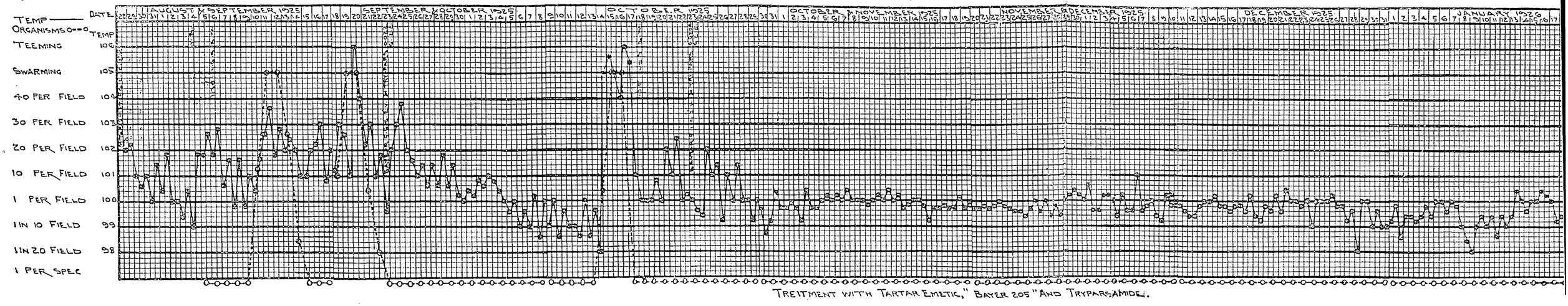
HORSE № 64. (1060 LBS. B.W.)

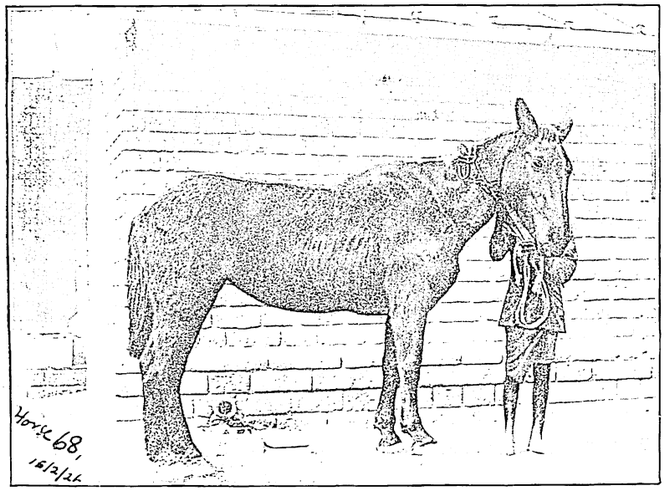


TREATMENT WITH TARTAR EMETIC. AND "BAYER 205"

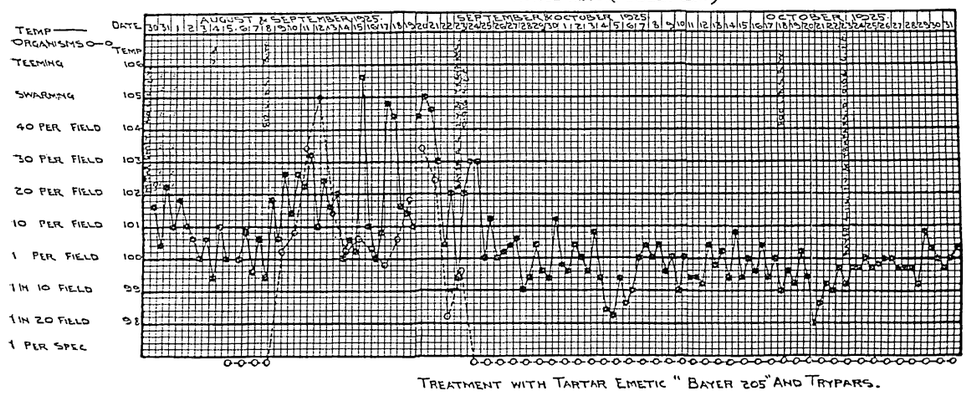


MARE No 68. (1120 LBS. B.W.)



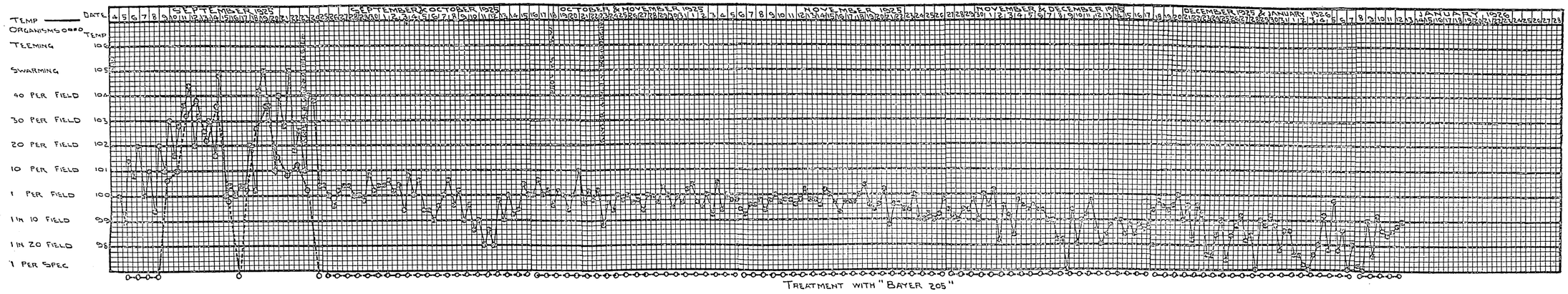


HORSE No 70. (796 LBS. B.W.)

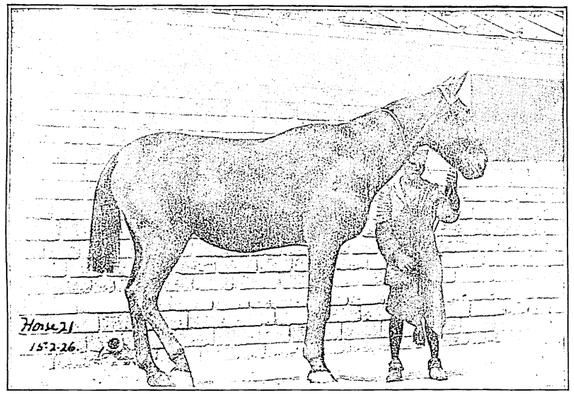


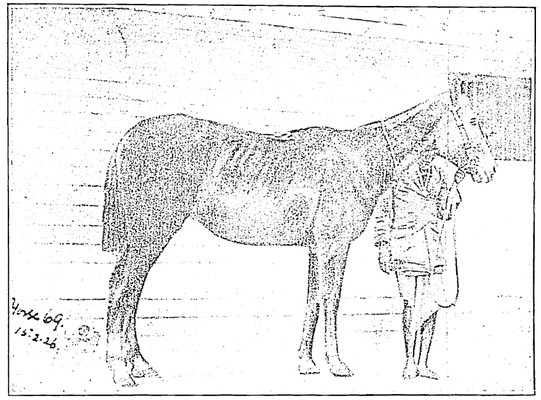
TREATMENT WITH TARTAR EMETIC " BAYER 205" AND TRYPARS.

HORSE Nº 69 (812 LBS. B.W.)

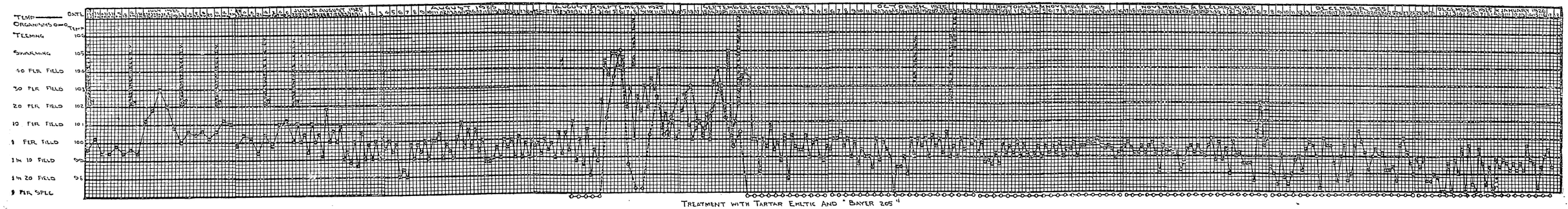


TREATMENT WITH "BAYER 205"

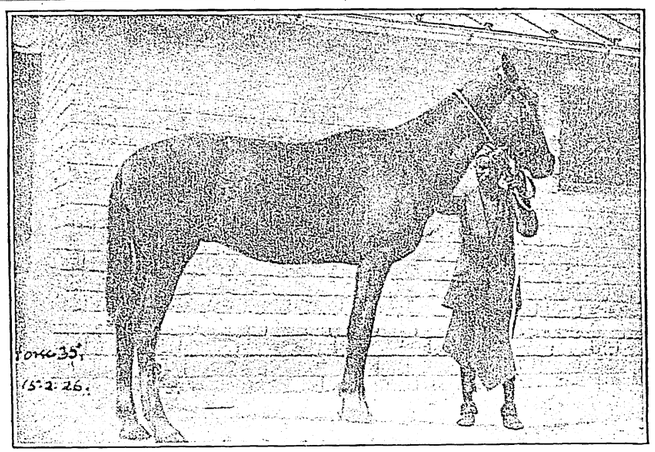




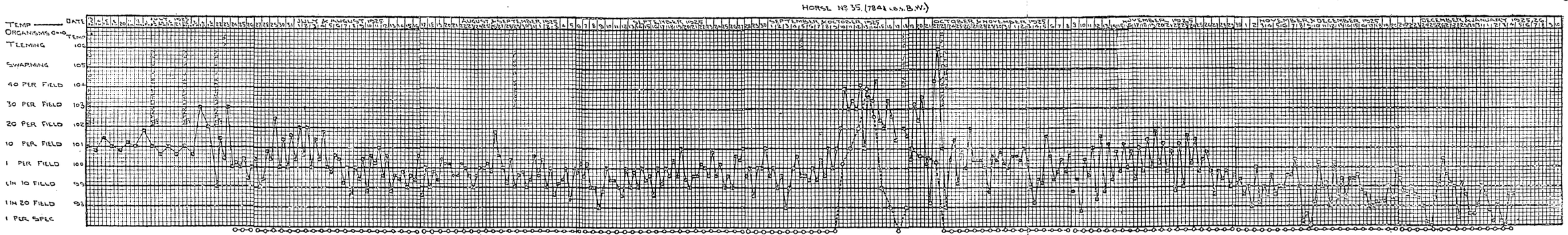
HORSE Nº 21 A (910 LBS. B.W.)



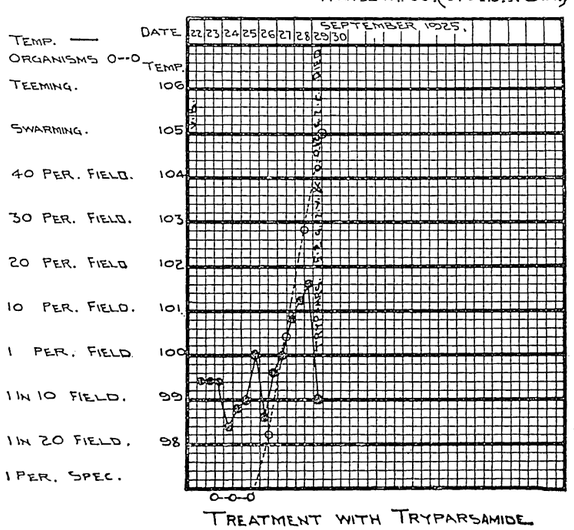
TREATMENT WITH TARTAR EMETIC AND "BAYER 205"

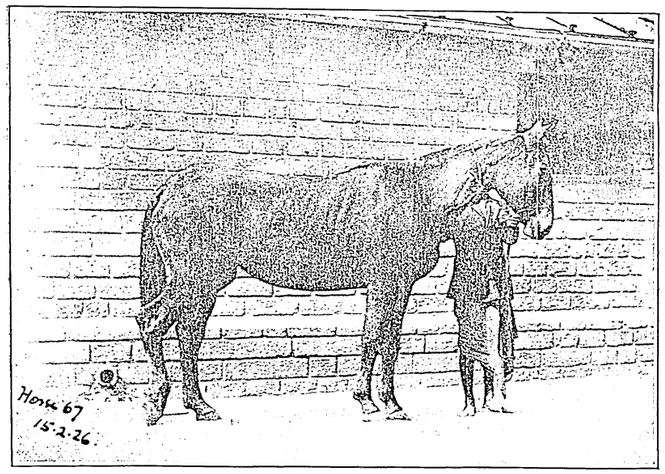


HORSE Nº 35. (784½ LBS. B.W.)

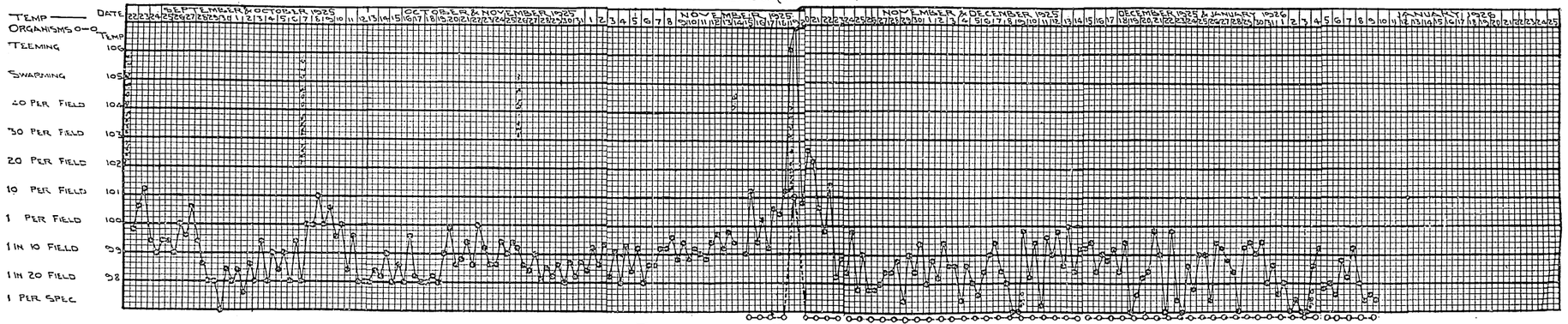


HORSE Nº 65. (570 L.B.S. B.W.)



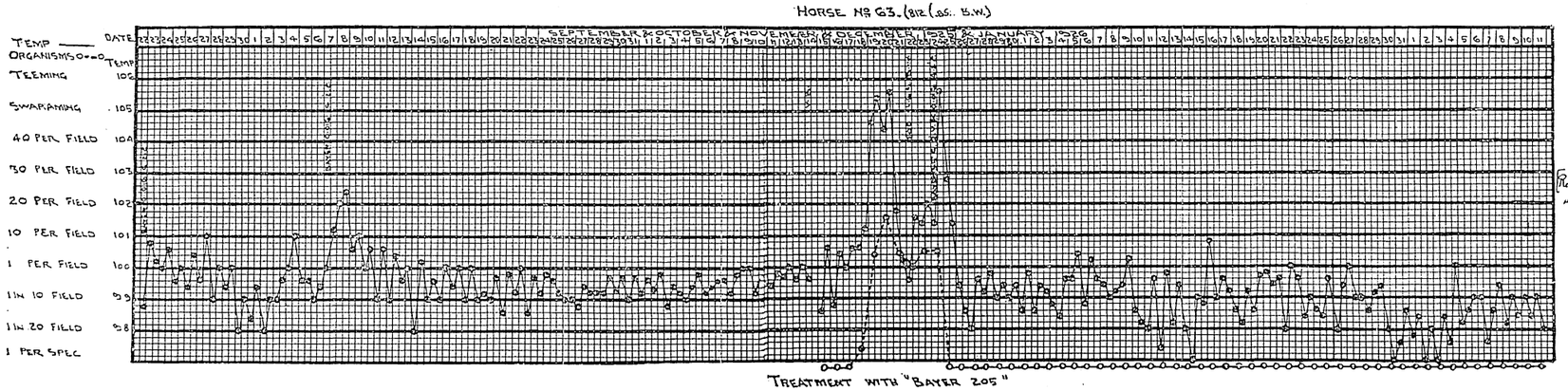


HORSE. Nº 67. (918 A.S.B.W.)



TREATMENT WITH TRYPAR—SAMIDE AND "BAYER 205"

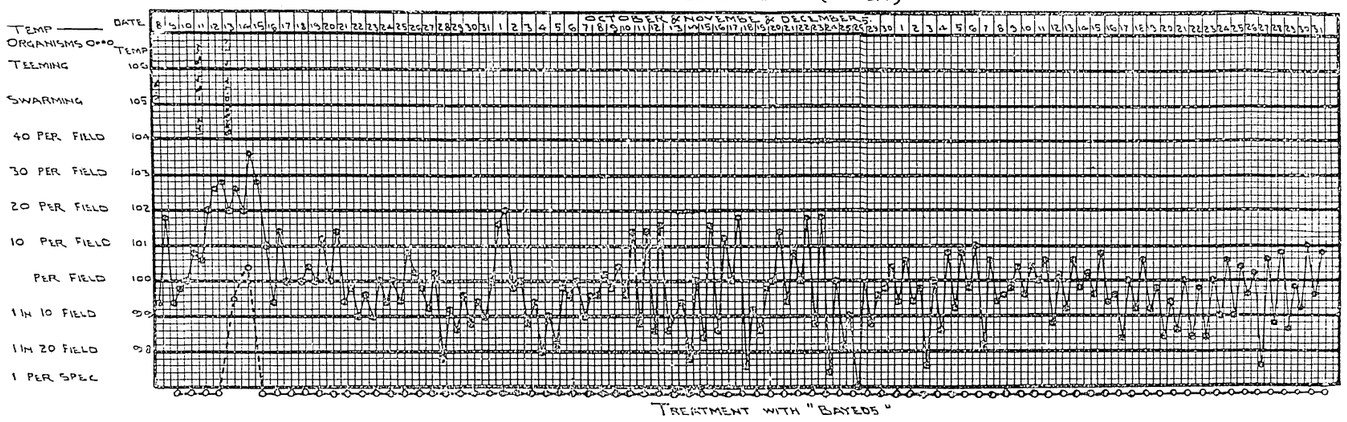
HORSE Nº 63. (812 A.S.B.W.)



[Relapsed 11th April 1926]

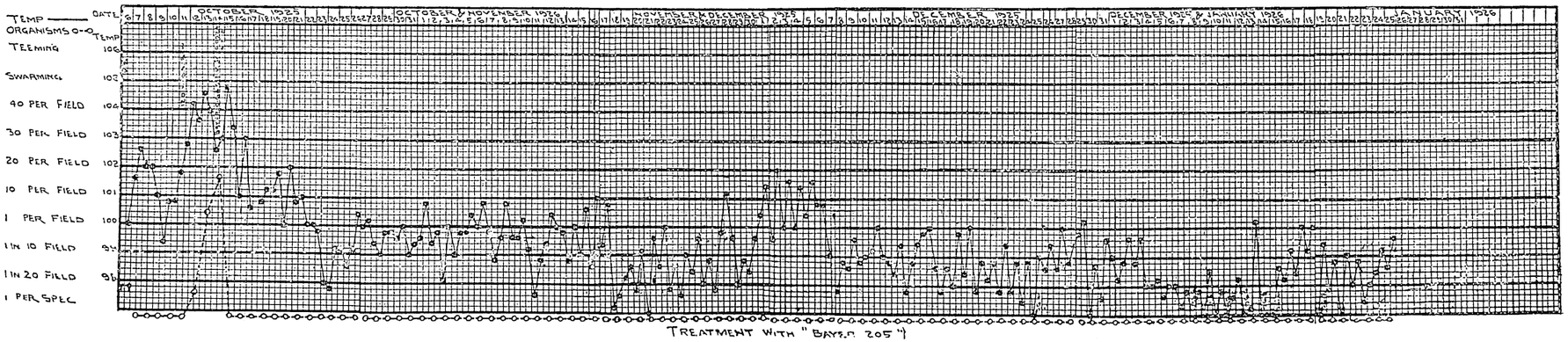
TREATMENT WITH "BAYER 205"

DONKEY Nº 41. (140 lbs. B.W.)



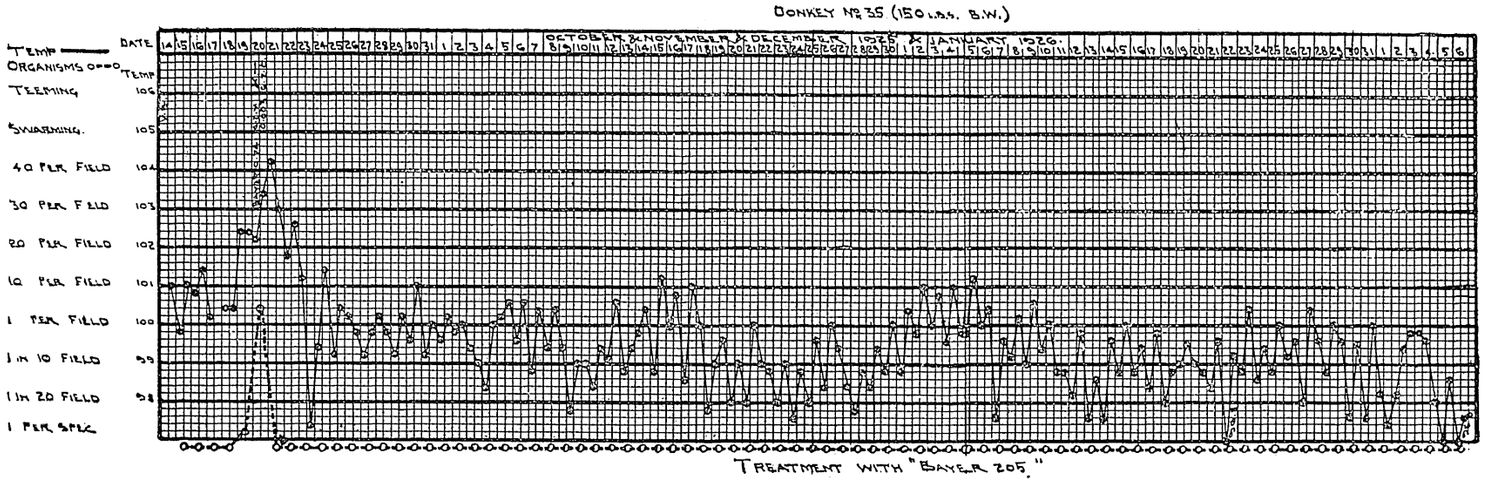
TREATMENT WITH "BAYER 205"

DONKEY Nº 36. (128 lbs. B.W.)



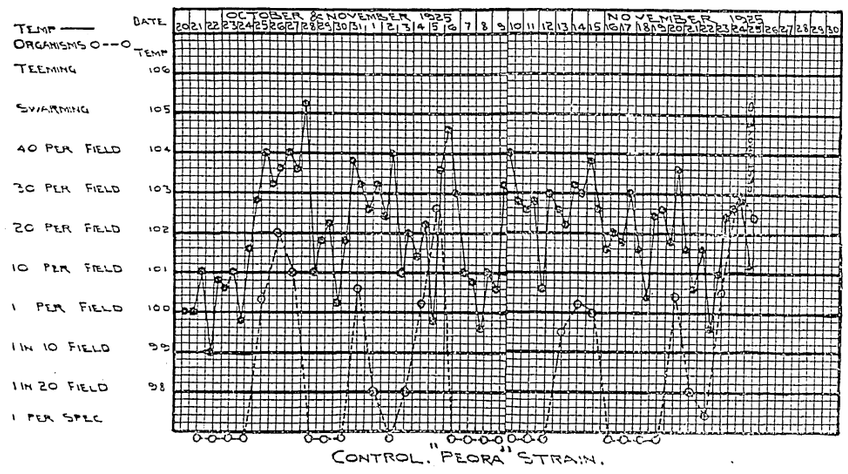
TREATMENT WITH "BAYER 205"

DONKEY Nº 35 (150 LBS. B.W.)



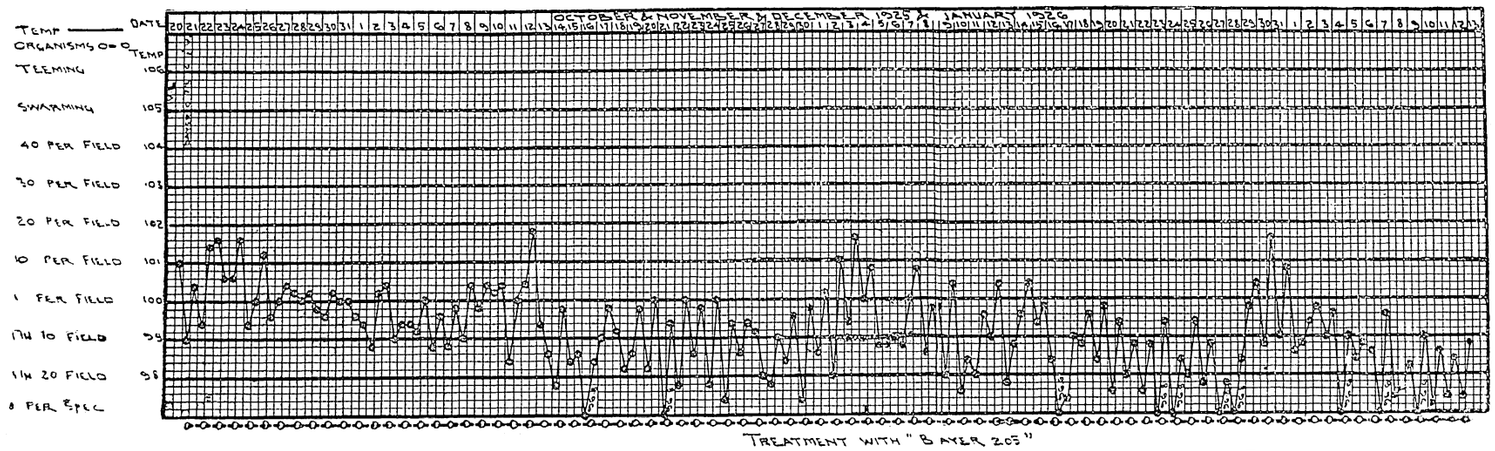
TREATMENT WITH "BAYER 205."

DONKEY Nº 28.



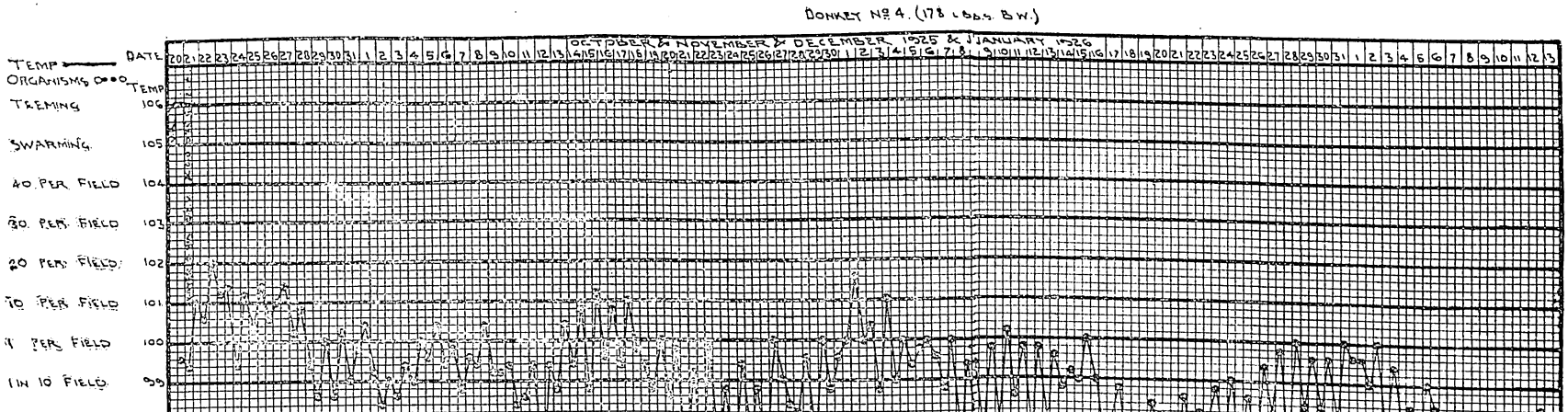
CONTROL. "PEORA" STRAIN.

DONKEY Nº 13. (146 LBS. B.W.)



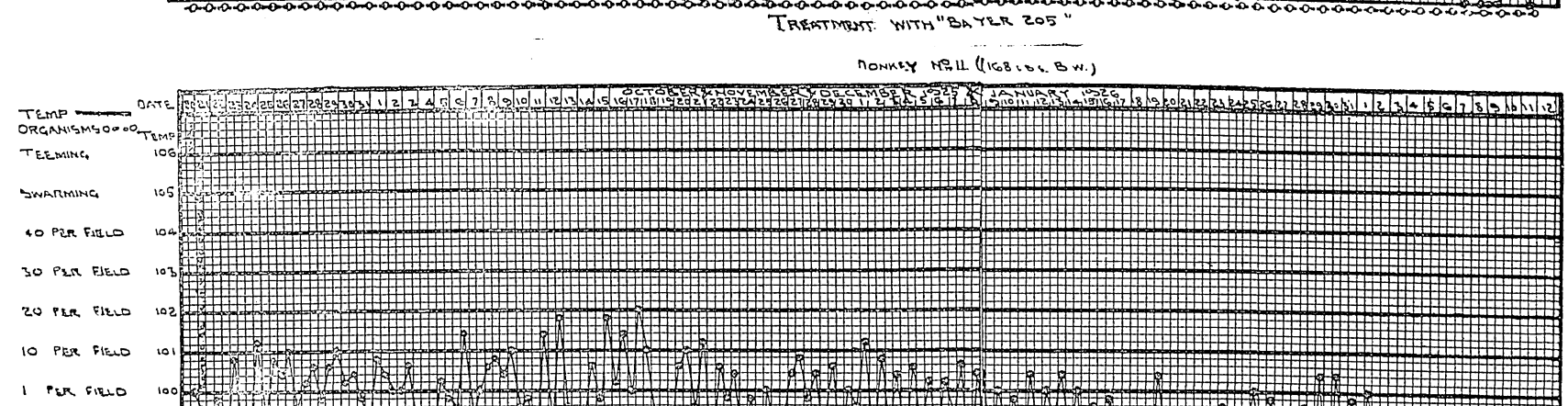
TREATMENT WITH "BAYER 205"

DONKEY No 4. (178 LBS. B.W.)



TREATMENT WITH "BAYER 205"

DONKEY No 11. (168 LBS. B.W.)



TREATMENT WITH "BAYER 205"

PLATE XVIII.

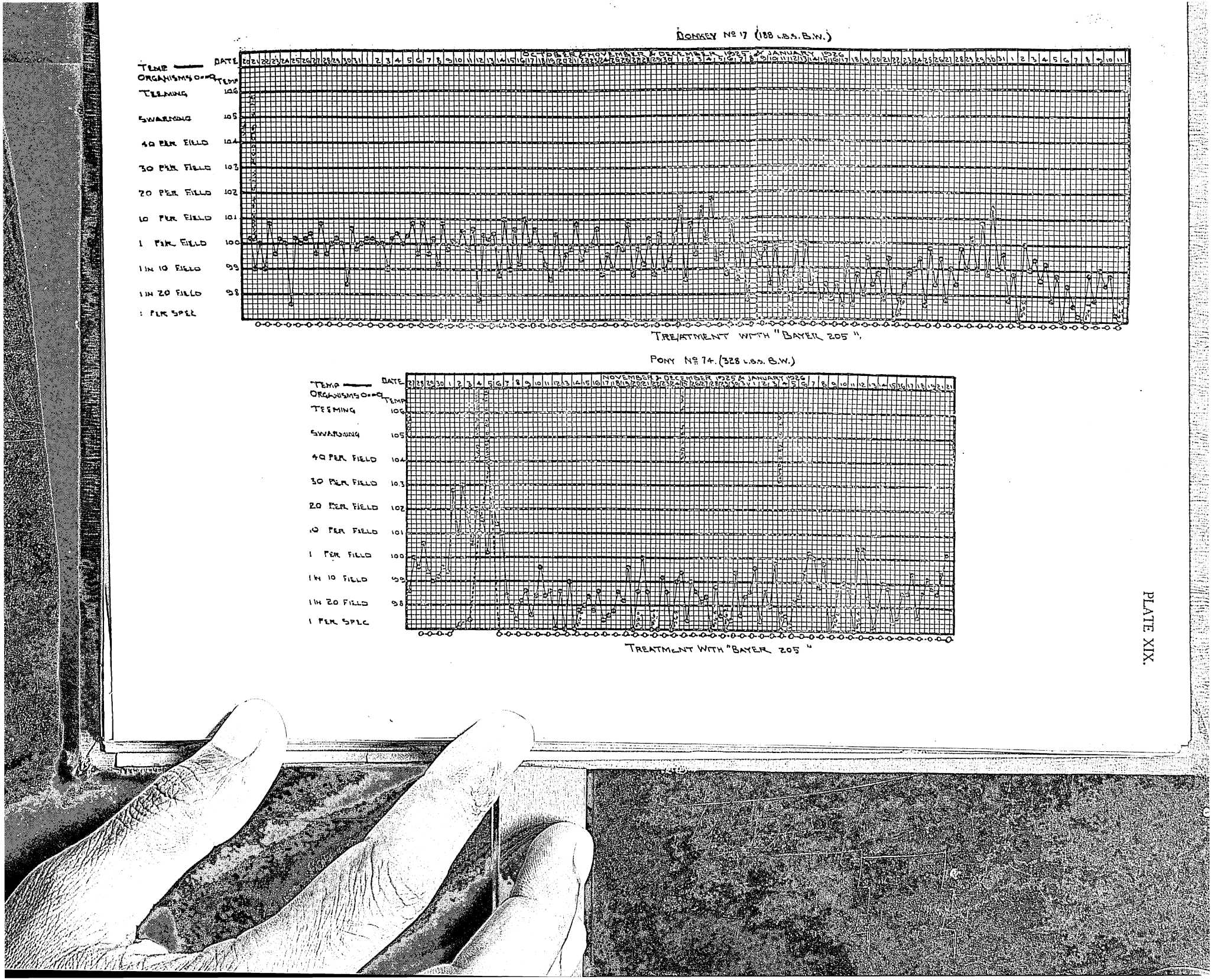

DONKEY Nº 17 (188 LBS. B.W.)
TEMP ——
ORGANISMS o--o
DATE
TEMP
TEEMING 106
SWARMING 105
40 PER FIELD 104
30 PER FIELD 103
20 PER FIELD 102
10 PER FIELD 101
1 PER FIELD 100
1 IN 10 FIELD 99
1 IN 20 FIELD 98
1 PER SPEC
OCTOBER & NOVEMBER & DECEMBER 1925 & JANUARY 1926
TREATMENT WITH "BAYER 205".
PONY Nº 74. (328 LBS. B.W.)
TEMP ——
ORGANISMS o--o
DATE
TEMP
TEEMING 106
SWARMING 105
40 PER FIELD 104
30 PER FIELD 103
20 PER FIELD 102
10 PER FIELD 101
1 PER FIELD 100
1 IN 10 FIELD 99
1 IN 20 FIELD 98
1 PER SPEC
NOVEMBER & DECEMBER 1925 & JANUARY 1926
TREATMENT WITH "BAYER 205"

PLATE XIX.

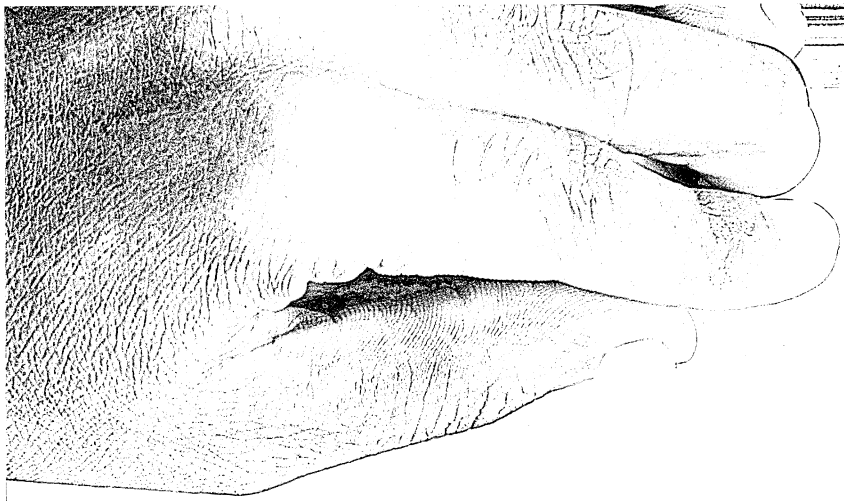
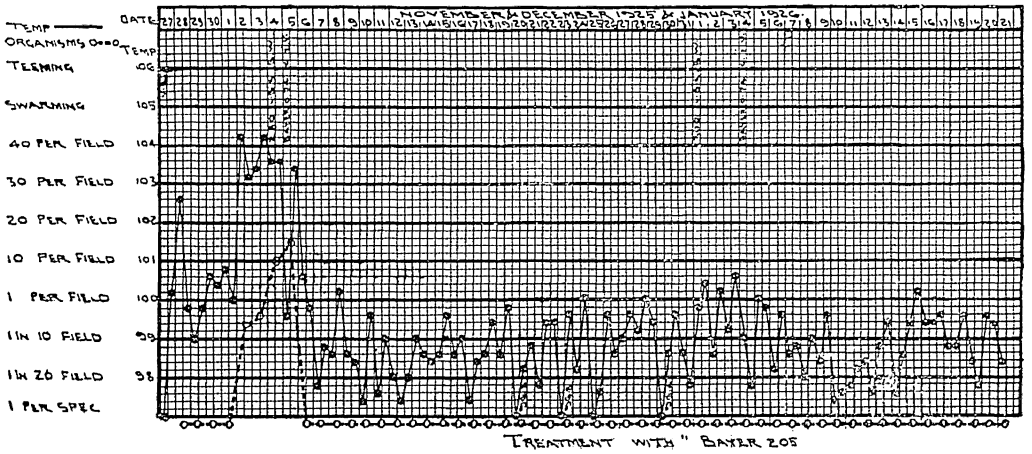
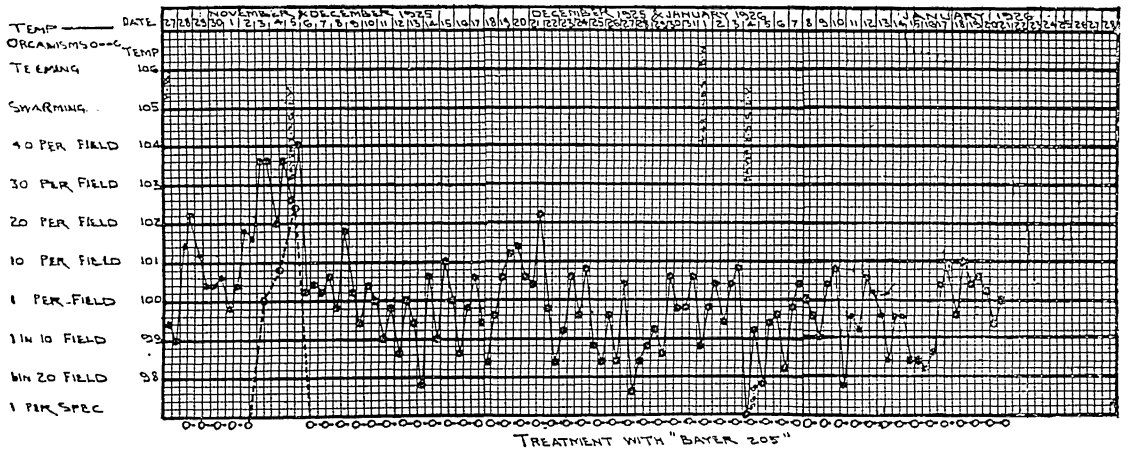


PLATE XX.

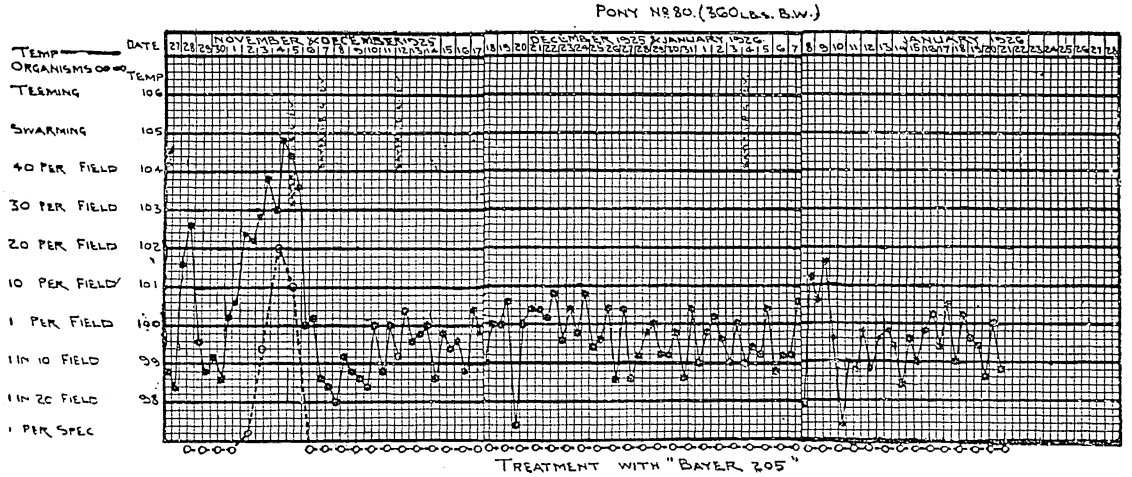
PONY MARE No 76 (298 Lbs. B.W.)

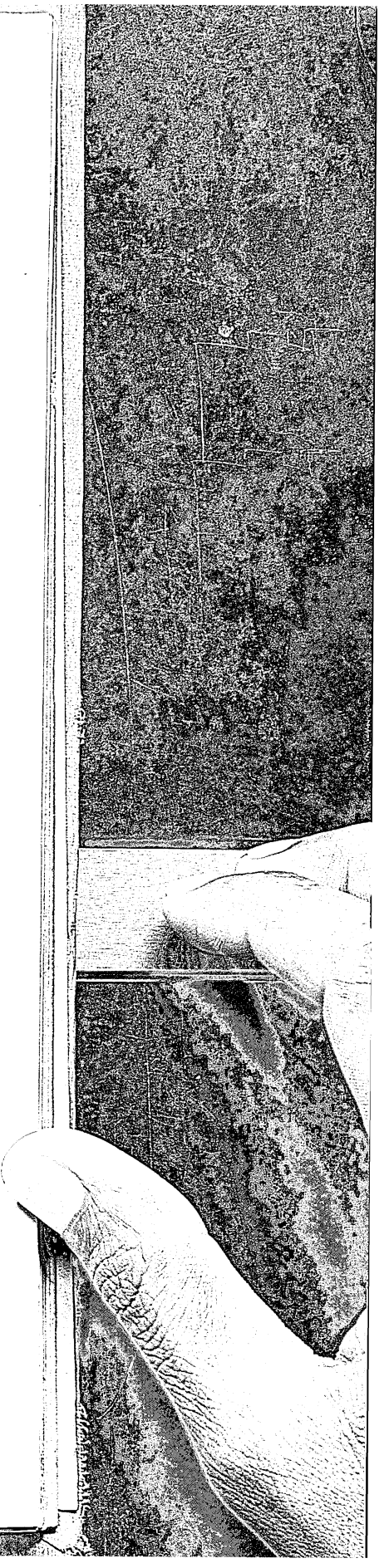


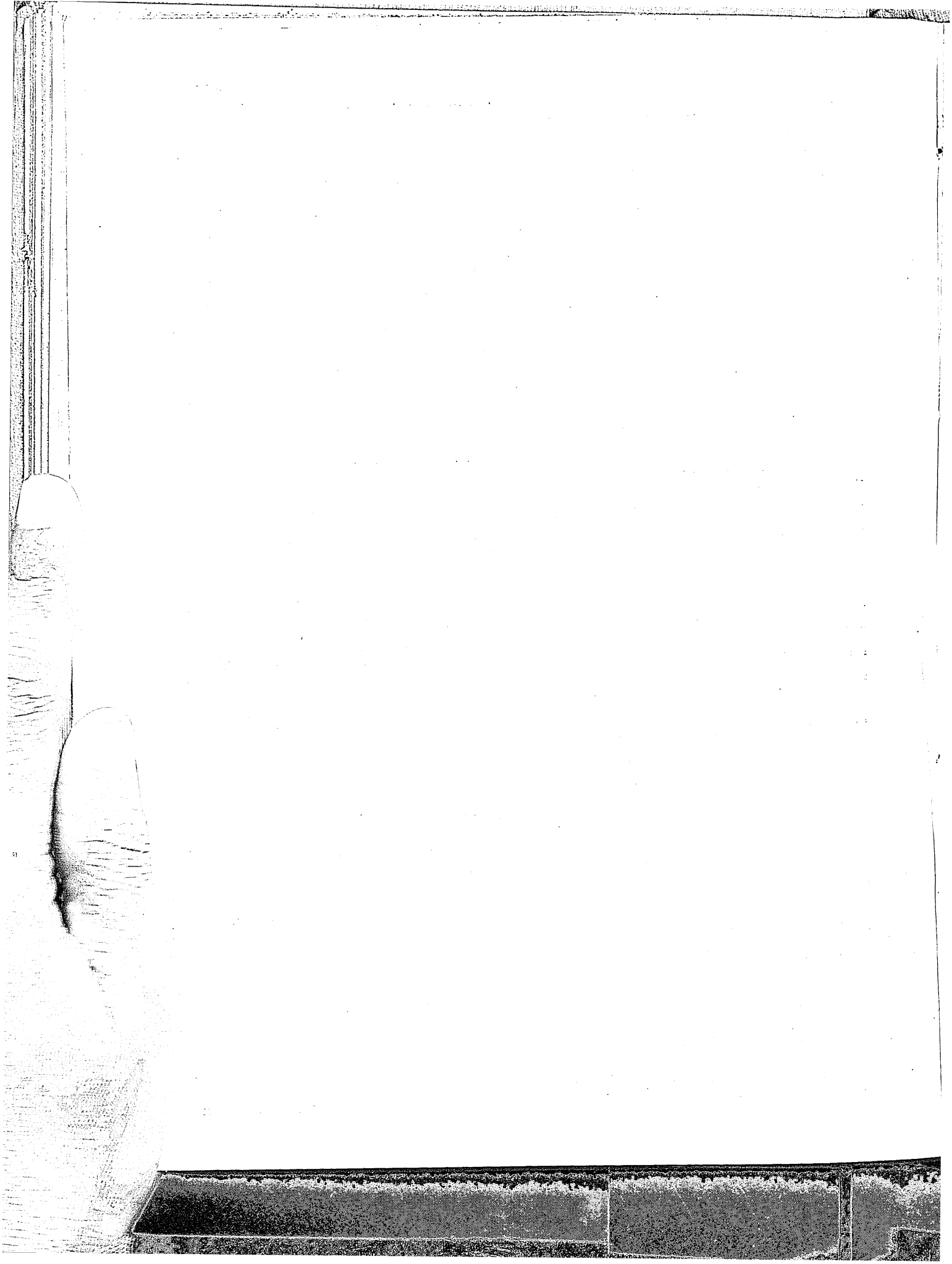
PONY No 79. (HGOWEN. B.W.)



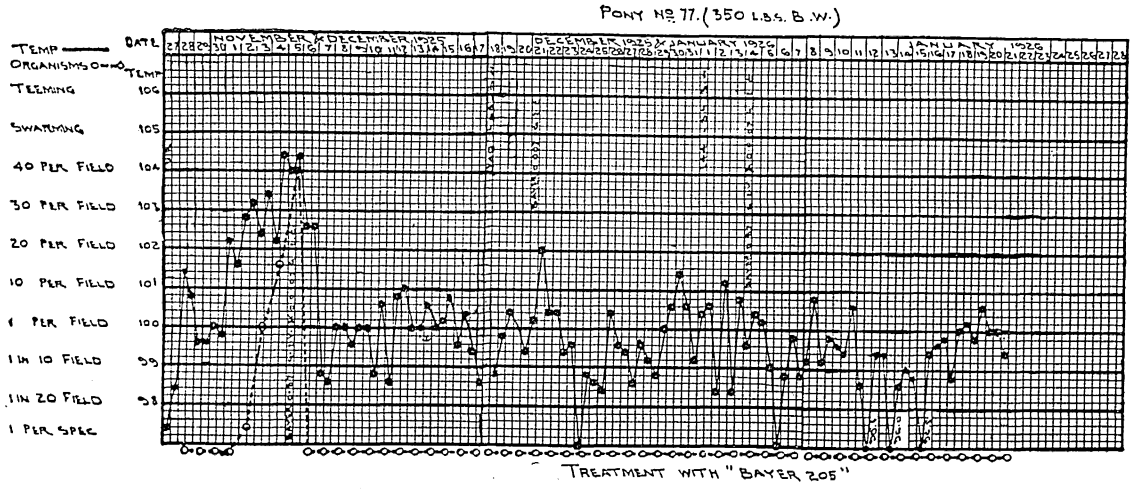
PONY No 80. (360 Lbs. B.W.)



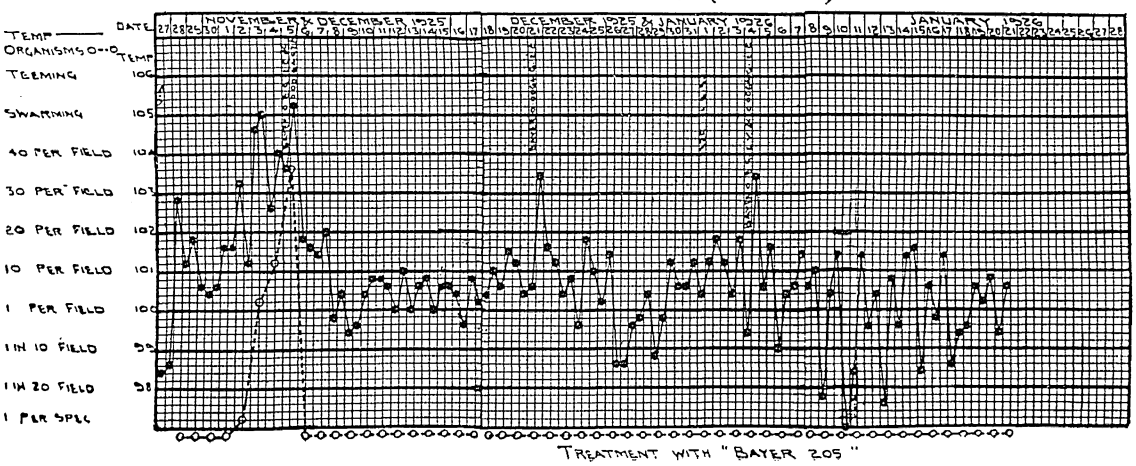




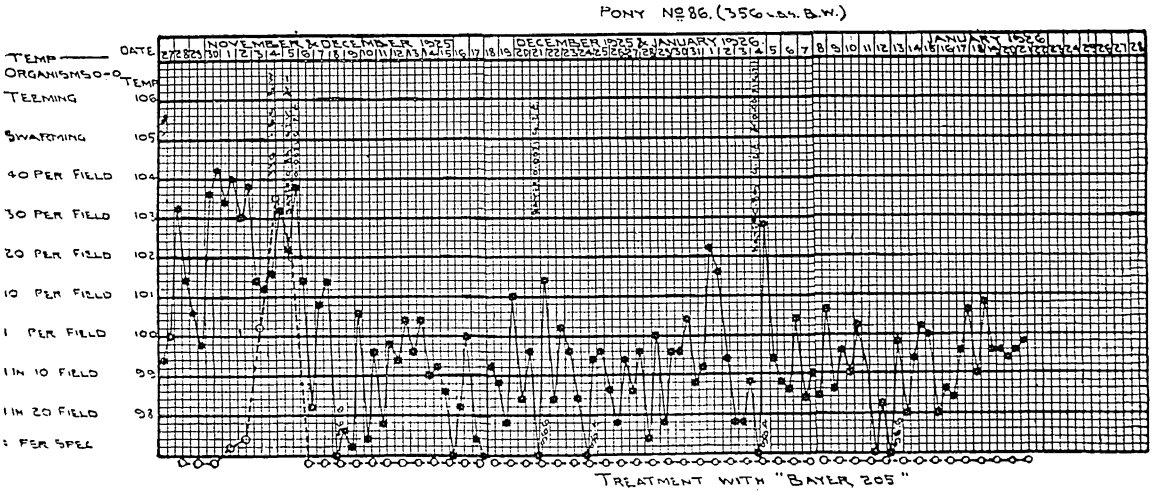
PONY Nº 77. (350 LBS. B.W.)



PONY Nº 78. (320 LBS. B.W.)



PONY Nº 86. (356 LBS. B.W.)



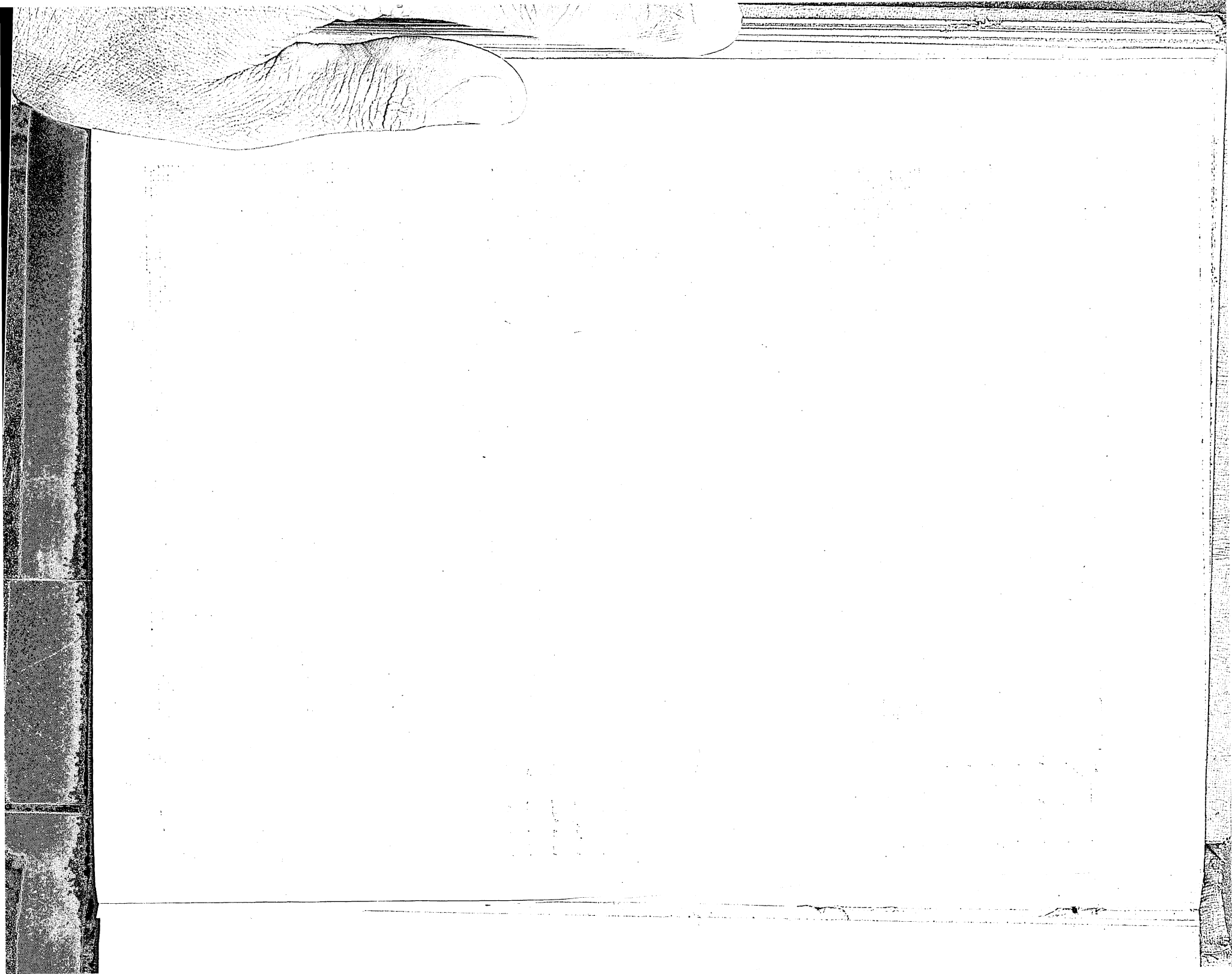
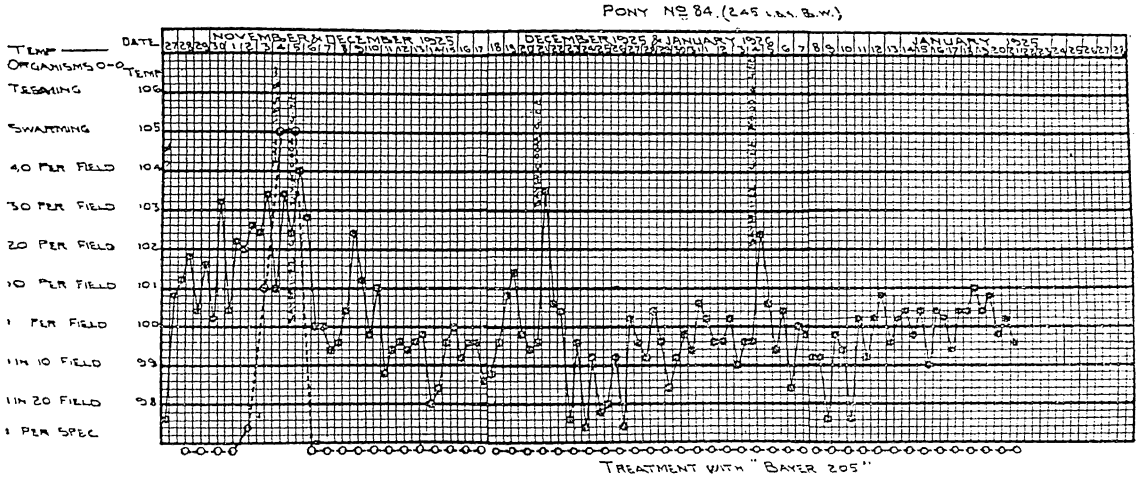
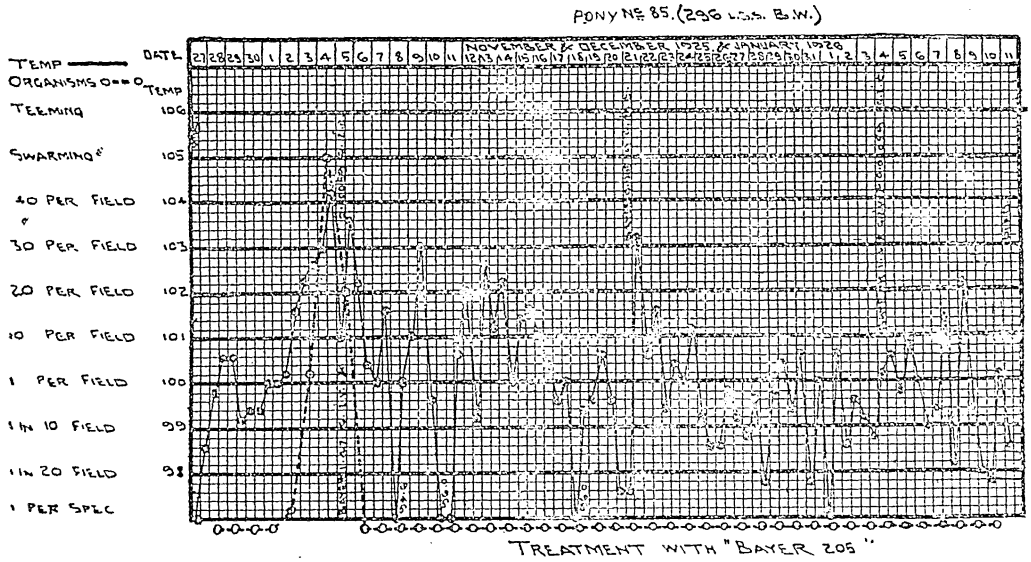
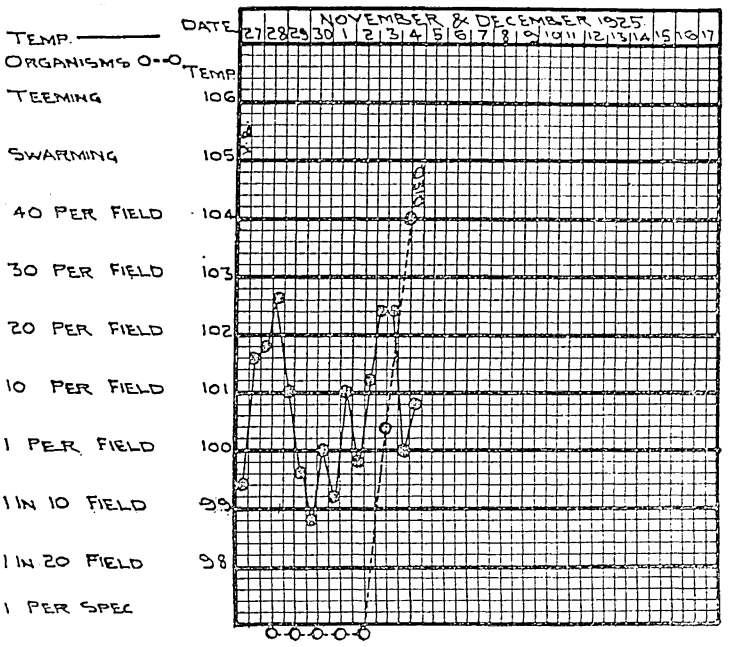


PLATE XXII


PONY Nº 84. (245 LBS. B.W.)
TEMP ——
ORGANISMS O-O
TEEMING
SWARMING
40 PER FIELD
30 PER FIELD
20 PER FIELD
10 PER FIELD
1 PER FIELD
1 IN 10 FIELD
1 IN 20 FIELD
1 PER SPEC
DATE
NOVEMBER & DECEMBER 1925
DECEMBER 1925 & JANUARY 1926
JANUARY 1925
TREATMENT WITH "BAYER 205"

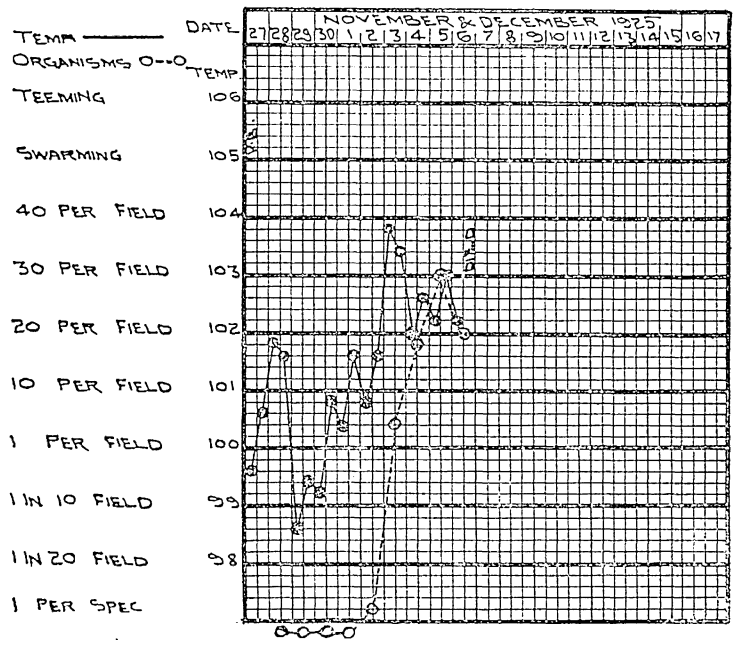

PONY Nº 85. (296 LBS. B.W.)
TEMP ——
ORGANISMS O--O
TEEMING
SWARMING
40 PER FIELD
30 PER FIELD
20 PER FIELD
10 PER FIELD
1 PER FIELD
1 IN 10 FIELD
1 IN 20 FIELD
1 PER SPEC
DATE
NOVEMBER & DECEMBER 1925 & JANUARY 1926
TREATMENT WITH "BAYER 205"

PONY Nº 83.

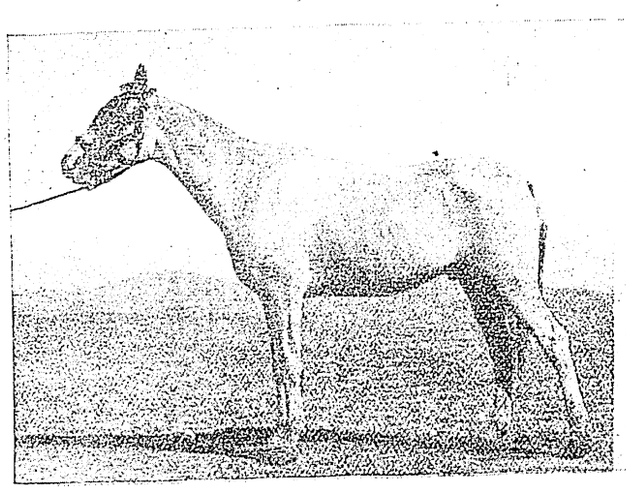


CONTROL ANIMAL- INJECTED WITH "PEORA" STRAIN SHOWING TRYPANOSOMES 12 PER FIELD.

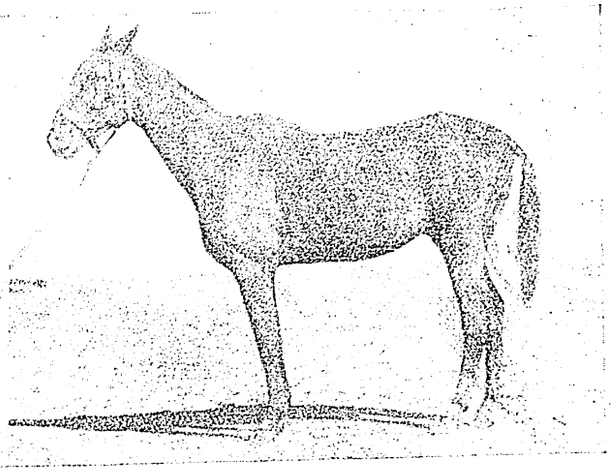
PONY Nº 82.



CONTROL ANIMAL- INJECTED WITH "PEORA" STRAIN SHOWING TRYPANOSOMES 12 PER FIELD.



Horse No. 51



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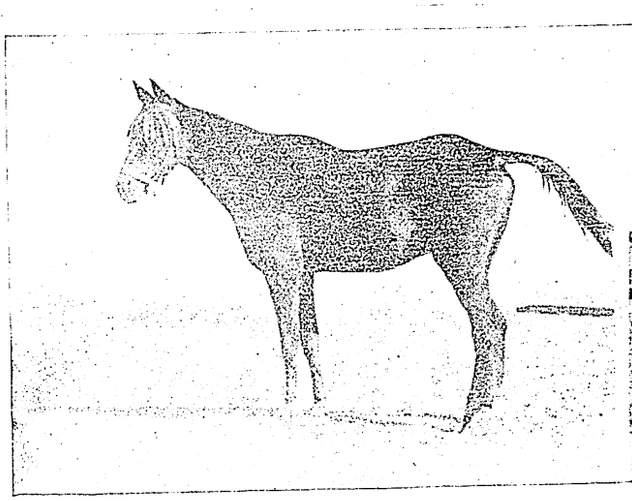

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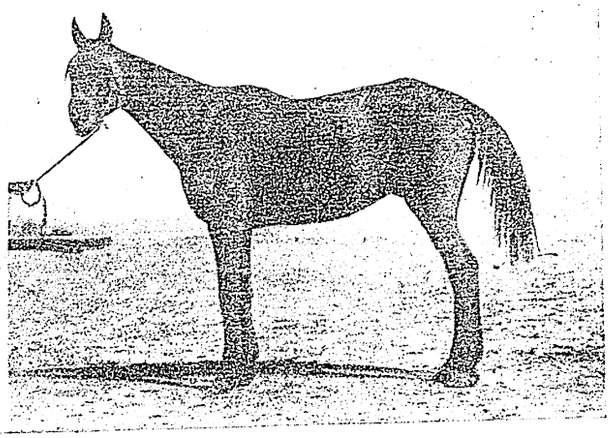

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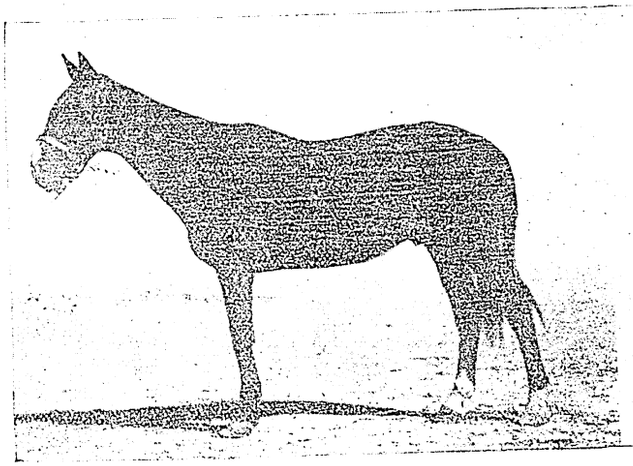

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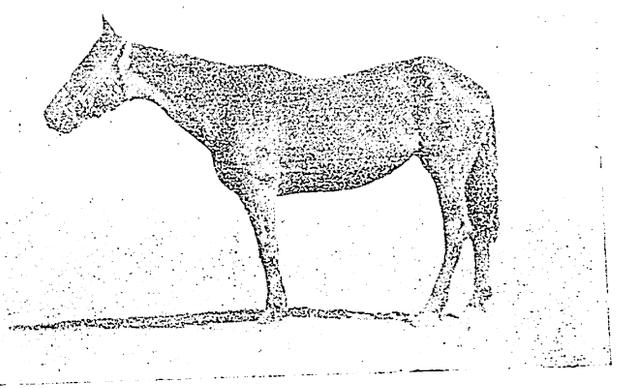

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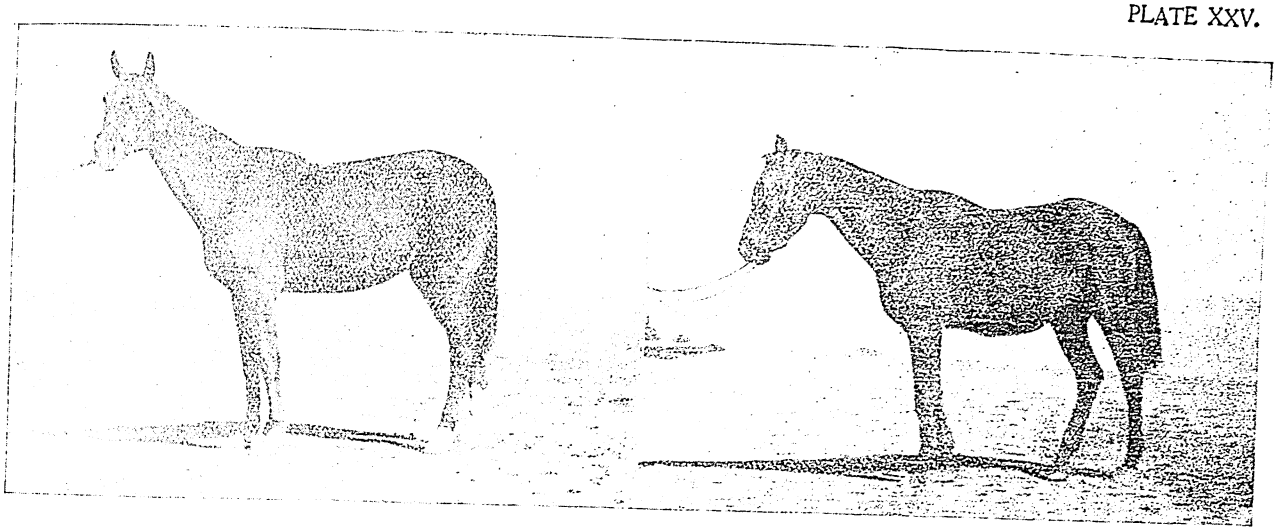
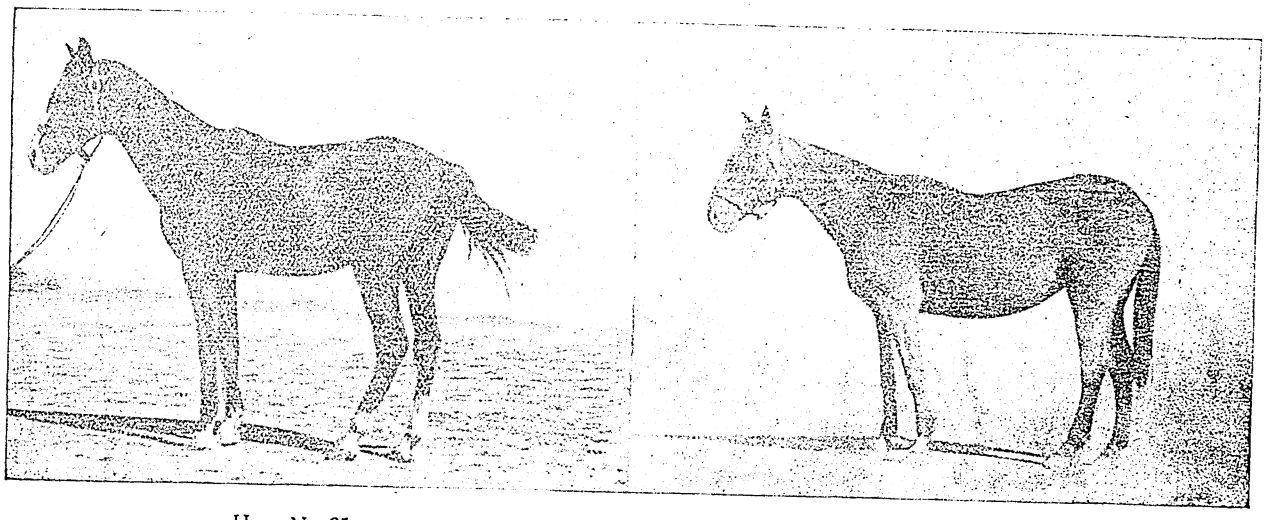


Horse No. 69.

Horse No. 21A.



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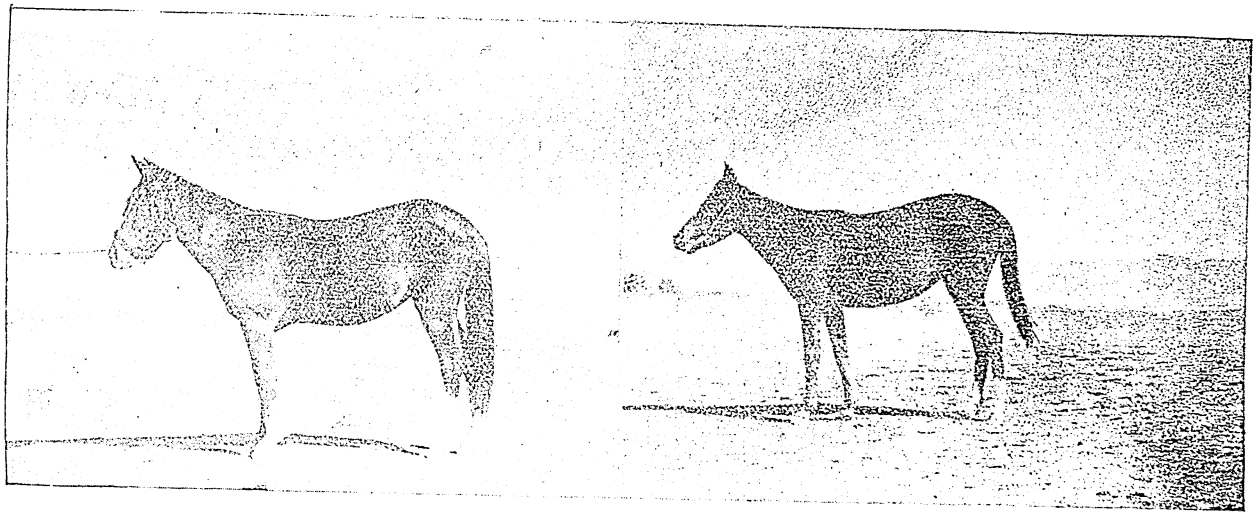

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Pony No. 80.

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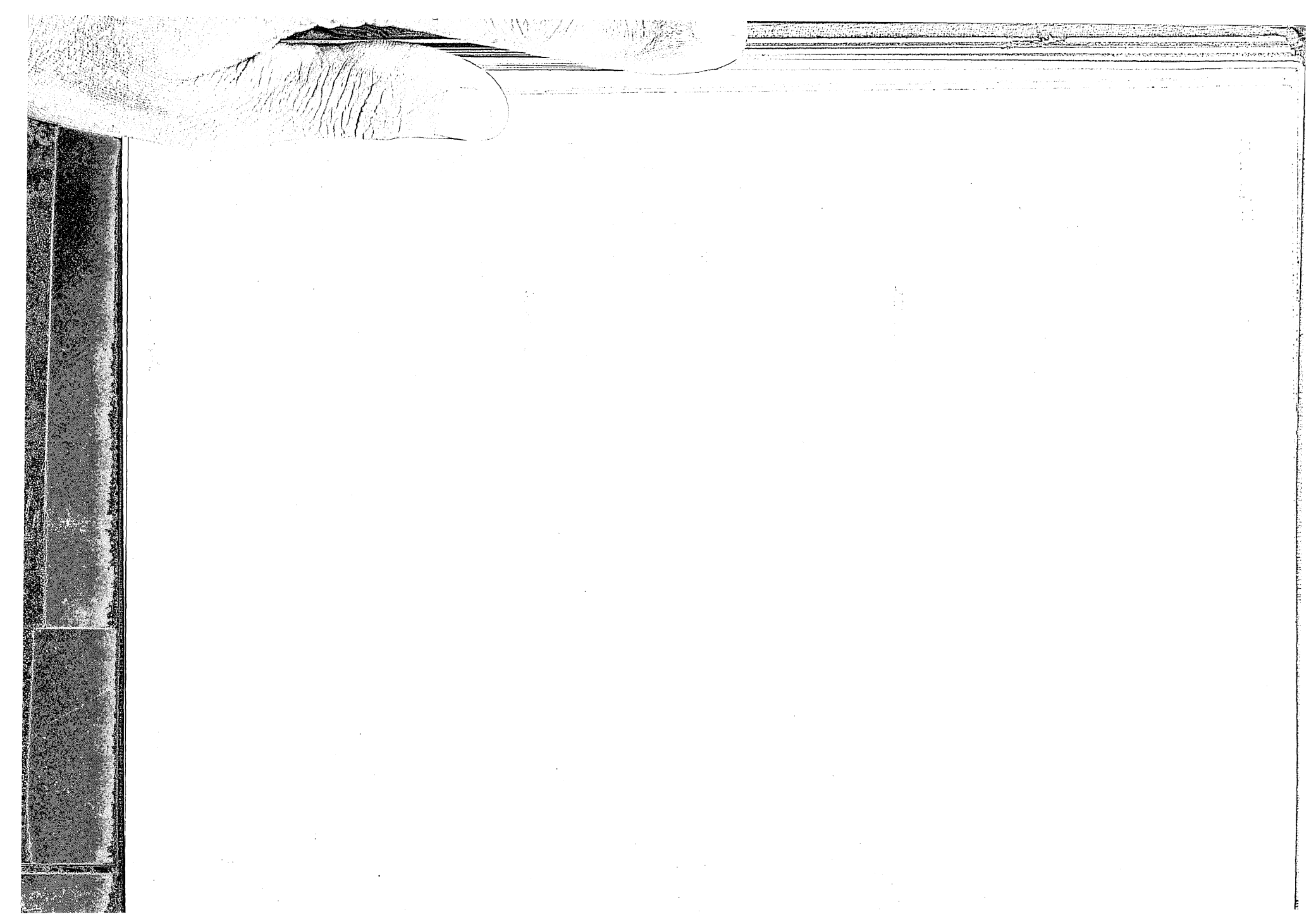

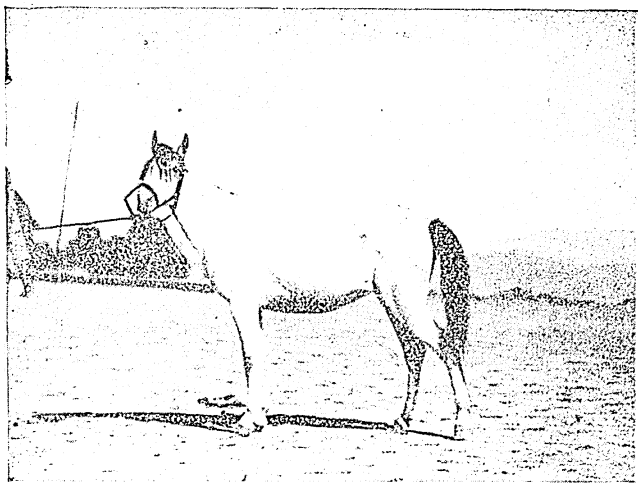

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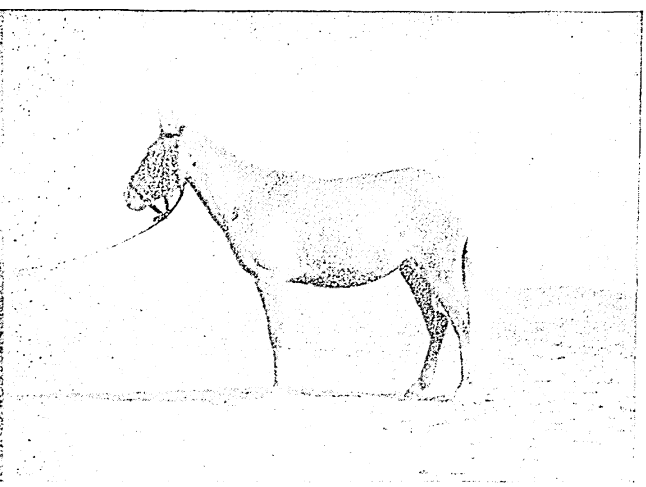

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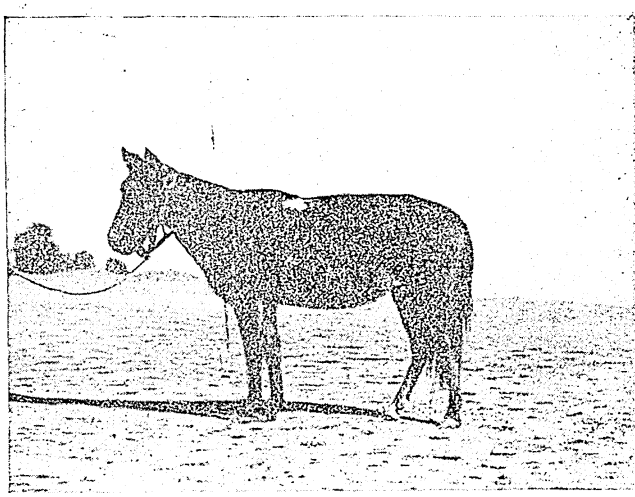

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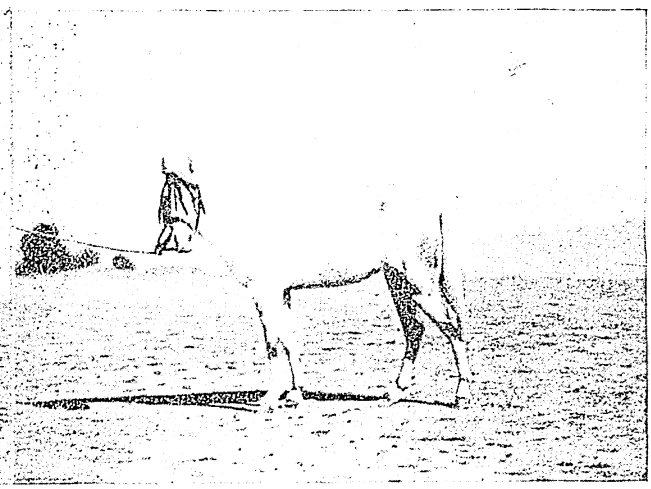

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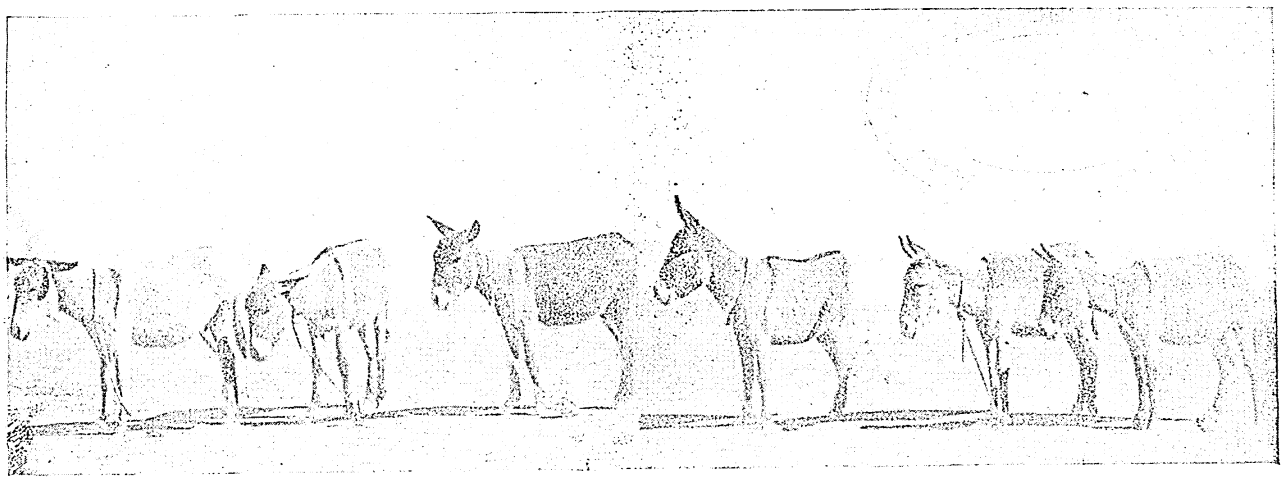

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Studies in Bovine Lymphangitis

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STUDIES IN BOVINE LYMPHANGITIS.

BY

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Bovine Lymphangitis, otherwise known as Infectious Lymphangitis, is one of the diseases commonly prevalent amongst cattle in India. The disease has been investigated in India by HOLMES (1908), RAYMOND (1909), and SHEATHER (1921).

HOLMES and RAYMOND investigated an outbreak of this disease which occurred in Calcutta among the Army Transport bullocks in the years 1906 and 1907, the former at the Imperial Bacteriological Laboratory, Muktesar, and the latter in Calcutta. The investigations were conducted independently of each other and the results arrived at by these workers are strikingly dissimilar.

HOLMES held the cause of the affection to be a streptothrix which he found not only in over three hundred smear preparations of pus from several cases but also in the sections of affected lymphatic glands. Histologically, he found in the lesions an extensive invasion of new connective tissue cells, epitheloid and a few giant cells.

On the other hand, RAYMOND held the cause of the disease to be a rod shaped organism with rounded extremities which he was able to isolate from less chronic cases. He has not, however, reported having found the organism in the smears of pus although he was able to isolate it in cultures from the pus and to reproduce, by inoculations of these cultures into animals, the same lesions as those observed by him in the naturally infected ones.

SHEATHER conducted his investigations at the Imperial Bacteriological Laboratory, Muktesar, from material sent by the Superintendent, Civil Veterinary Department, Madras, in November 1918 and July 1919, from affected cattle and a report of his investigations was published in the *Mem. Dept. Agri. India, Vet. Ser.*, Vol. III, No. 3, May 1921. SHEATHER has reviewed fully the results arrived at by the above workers as well as other previous literature bearing on the subject, namely, by NOCARD (1888) and VRYBURG (1907) and has finally come to the conclusion that the

causative agent agrees in the majority of its characters with those observed by VRYBURG and RAYMOND approximating most closely to the Preisz-Nocard bacillus but differing from it in being Gram—negative.

In view of the different opinions, held by HOLMES and RAYMOND, regarding the cause of the disease and as SHEATHER's report had not been published at the time, I set myself under instructions from Mr. AITCHISON, the then Principal of the Madras Veterinary College, to investigate an outbreak of this disease which occurred among cattle belonging to the Madras Corporation, in August 1920. The observations and experiments made by me in connection with the investigation of the outbreak and subsequently form the subject of this paper.

History.

The disease was first noticed in Madras in the year 1909 among the bullocks employed for the conservancy work of the Madras Corporation and appears to have existed among them till about 1912. Subsequently, in August 1920, the disease was again observed in a bullock in one of the depots and the infection spread therefrom to three other depots.

Symptoms.

During the period between August 1920 and November 1922, as many as 234 animals were affected in four of the depots A, B, C, D, of which 55 were sent over to the Madras Veterinary College hospital for treatment and the rest were treated by the Corporation Veterinary Officer at the depots. The symptoms shown by these animals were exactly similar to those described by HOLMES and RAYMOND in the animals that came under their observation and to those reported to have been exhibited by the animals from which materials were sent to SHEATHER for investigation.

The first observable symptom in this disease is the appearance of a nodular enlargement of one or more of the superficial lymphatic glands especially in the region of the flap of the flank or in front of the shoulder or very occasionally in other parts of the body. The affected animals inspite of such enlargements evince neither pain nor inconvenience and perform their usual work. In the course of two to three weeks, the nodules considerably increase in size and, in some animals, become tense and indurated.

In the cases which are allowed to run their course, the affected glands pit on pressure and indicate the existence of pus which has more or less disorganised them. No signs of acute inflammation in the regions of these glands nor of marked constitutional disturbance are noticed ; but if the glands are considerably enlarged, slight lameness is discernible either in the fore leg or in the hind leg, accord.ng as the prescapular or the precrural gland is affected. In some instances, as a result of the

blocking up of the lymph vessels, small abscesses in the form of buds are noticed extending in a centrifugal direction.

Usually, the general condition of the animals is not much affected, though in some animals general emaciation and debility become very marked with the advancement of the disease and in others symptoms of respiratory affection are very prominent, indicating affection of the lungs. (Pl. I, Fig. 1.) With the further advancement of the disease, paroxysms of cough and difficulty of breathing may become more insistent and the animals eventually die of catarrhal pneumonia with pulmonary infarction and abscesses in the lungs.

Mode of infection.

In order to explain, what I believe to be the mode of infection in this disease, it is necessary to review the distribution of the various lymphatic glands in the body and the respective areas drained by them and to discuss briefly the opinions expressed by previous workers on this aspect of the question. The glands that are found to be involved in this disease are those that are concerned in draining the skin area of the body. Their study will therefore be dealt with in detail; for the purpose of this paper, I have adopted the following classification* of the areas drained by these glands.

A.

1. *Area of the skin of the face in part* is drained by the submaxillary (mandibular) lymph glands. In addition, these glands receive afferent vessels from the muzzle, lips, cheeks, hard palate, the anterior part of the turbinates and septum nasi, the gums (in part); the sublingual and parotid glands; the tip of the tongue; the muscles of the head except those of the eye, ear, tongue, and hyoid bone; the mandible, premaxilla and nasal bone.

The efferent vessels, two to four in number, go to the atlantal gland.

2. *Area of the skin of the head in great part* is drained by the parotid lymph gland. In addition, this gland receives afferent vessels from the muzzle, lips, the gums (in part); the anterior part of the turbinates and septum nasi; the parotid salivary gland; most of the muscles of the head including those of the eye and ear; the eyelids, lachrymal gland and external ear; the frontal, malar, nasal, and premaxillary bones and the mandible.

The efferent vessels of this gland also go to the atlantal gland.

N.B. The efferent vessels of the atlantal gland, three to six in number on each side, concur in forming the tracheal lymph duct.

B.

Area of the skin of the neck, shoulder, part of the ventral and lateral surfaces of the thorax, and the thoracic limb is drained by the prescapular (posterior superficial

* Adopted from Sisson's Anatomy of the Domestic Animals (2nd Edition, 1914).

cervical) lymph gland. In addition, this gland receives afferent vessels from the muscles of the shoulder girdle and from the external scapular muscles; from the tendons of the muscles of the forearm and digit and the fascia of the forearm; from the joints of the carpus and digit.

The efferent vessel of the right prescapular gland opens into the end of the right tracheal duct, while that of the left gland opens into the terminal part of the thoracic duct or the left tracheal duct.

C.

Area of the skin of the posterior part of the thorax, the abdomen, pelvis, thigh and leg is drained by the precrural (prefemoral or subiliac) lymph gland. In addition, this gland receives afferent vessels from the tensor fasciæ latæ and the prepuce.

The efferent vessels end chiefly in the deep inguinal gland, but in some cases some go to the iliac glands.

N.B. Two small and inconstant nodes, one or two in number, the paralumbar lymph glands may be found under the skin of the upper part of the flank. Their afferent vessels come from the adjacent skin, and the efferents go in part to the prefemoral gland, in part to the deep inguinal gland.

D.

Area of the skin of the medial and posterior surface of the thigh and medial surface of the leg is drained by the superficial inguinal lymph glands. In addition, these glands receive afferent vessels from the external genital organs (except the testicles) in the bull.

The efferent vessels go to the deep inguinal gland.

E.

Area of the skin of the hip and tail is drained by the ischiatic lymph glands.

In addition, these glands receive afferent vessels from the rectum and anus, the vulva, the root of the penis, the prostate, the bulbo-urethral glands, the urethra and urethral muscle, the glutei, biceps femoris, semitendinosus, obturator internus, and gemellus and the lumbodorsal fascia; the hip joint; and the efferent vessels of the popliteal gland.

The efferent vessels go to the internal iliac lymph glands.

N.B. The efferents from the internal iliac glands go to the lumbar trunk and those from the deep inguinal glands go in part to the internal iliac glands and in part directly to the lumbar trunk.

From a study of the anatomical relations of the lymphatic glands noted above, it will be seen that there is absolutely no direct intercommunication whatever between the superficial lymphatic glands concerned in draining the several skin areas, A, B, C, D and E of the body. Each set of these glands empties itself either into the lymphatic duct directly, or communicates with other glands whose efferents empty themselves in turn into the duct.

From Plate II, it will further be seen that the precrural glands drain the largest skin area, the prescapular a fairly large area, while the submaxillary, parotid, superficial inguinal and ischiatic glands collectively drain only a very small area.

The mode of infection will now be dealt with.

SHEATHER has not dealt with this aspect of the problem in his paper.

In dealing with the symptoms, HOLMES writes as follows :—

" The first symptom which attracted attention was usually the appearance of a small nodule under the skin in the region of the neck, shoulder, ribs or flank. This was followed after a period varying from a few days to some weeks by an enlargement of the deep seated glands, almost invariably the prescapular or precrural.

This was accompanied by pain and inflammatory swelling in the affected part and generally marked lameness.

The affected subcutaneous lymphatic glands varied in size from a pea to a walnut. The precrural glands reached the size of a cricket ball, while the largest prescapular gland observed was more than six inches in diameter.

* * * * *

In all except one, the disease followed a wound or sore in the region of the neck or hump. These sores are locally known as ' Calcutta sores '. They are indolent, spreading and very difficult of treatment. In one instance, the popliteal gland became affected after a wound between the digits of the hind foot."

RAYMOND states as follows :—

" It (the disease) appeared to originate through the infection of a wound, at least, in the cases which came to this College, numbering 11 in all, a wound of some kind, generally a yoke gall, was present. This lesion was sometimes a simple abrasion, at others an important sore, which in some cases was complicated by a considerable tumifaction of the parts and lameness ".

Neither HOLMES nor RAYMOND has given a classified list of the glands affected in the animals which came under their observation, although it will be seen from their reports and the photographs appended to them that only the superficial glands concerned in draining the several skin areas as classified by me were found to have been involved. Chart I represents graphically the number of animals affected in the outbreak investigated by me, classified according to the glands involved.

The excerpts quoted above from the contributions of HOLMES and RAYMOND would appear to suggest :—

1. that the primary affection generally follows a yoke gall, ro sore in the region of the neck or hump and
2. that from such seats of primary affection, the infection spreads and affects not only the prescapular glands but also other superficial glands of the body.

But the facts which have come under my notice suggest different conclusions. Of the animals that were treated at the College hospital and in the Corporation depots during the outbreak of 1920-1922 only a few had any yoke gall, sore or apparent abrasion in the region of the neck or hump or anywhere else in the body. Even in these few animals, no eulargements of the lymphatic vein connecting an infected gland with a pre-existing yoke gall, sore or abrasion, as recorded by Raymond, to which the possibility of a primary infection could be traced were observed by me.

From the details of inoculation experiments recorded by SHEATHER, it would also appear that every subcutaneous inoculation of either pus emulsion from original cases or broth culture made from the pus, in hill bulls and plains calves in the region of the neck led to the affection of the prescapular gland only. No mention has been made of any other glands having been affected.

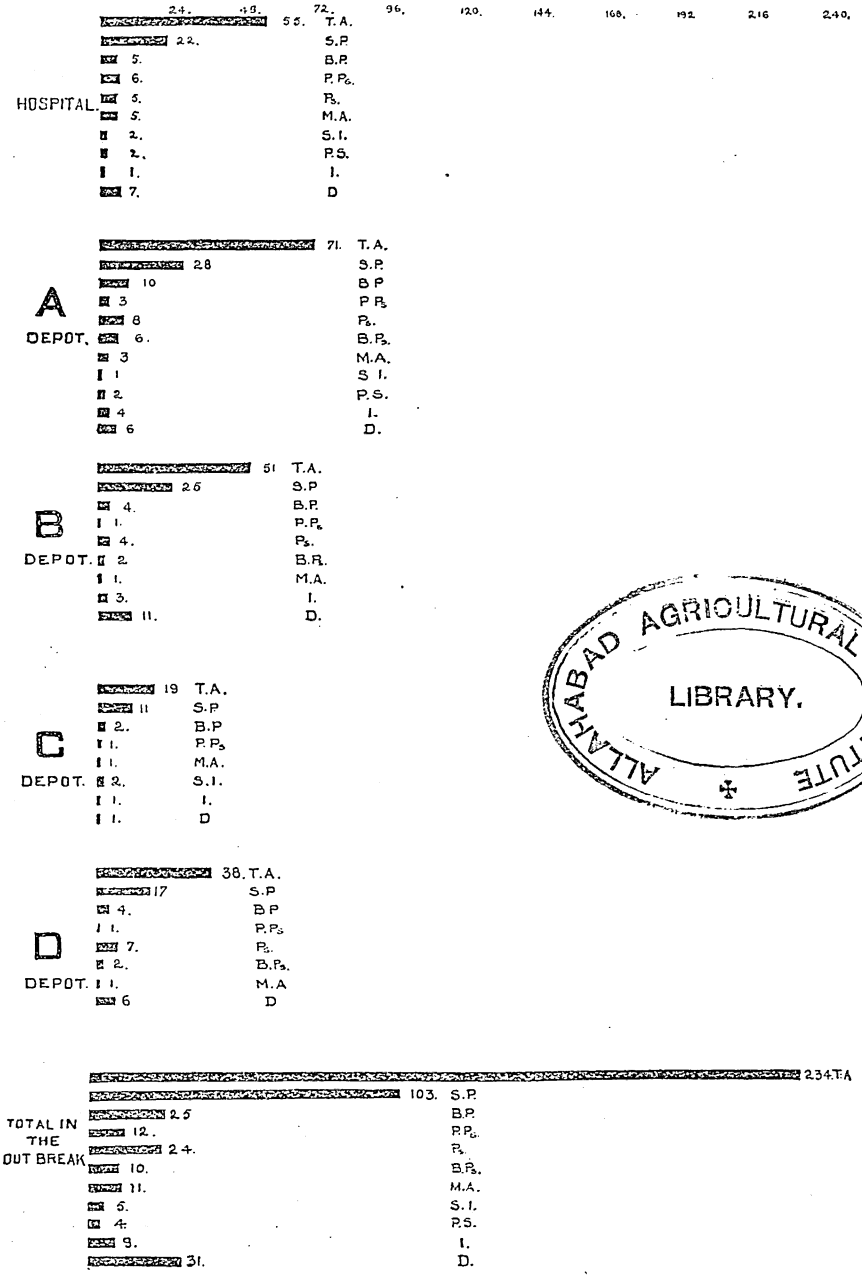
Further, if, as HOLMES and RAYMOND appear to have supposed that the infection had originated from a yoke gall or from an indolent tumified sore or abrasion pre-existing in the region of the neck, only the prescapular glands or perhaps the more deep seated glands of the region of the neck would have been affected but not the precrural or other superficial glands of the body. The infection could not have spread to these latter glands from the primary focus without other lymphatic glands *en route* having been involved, inasmuch as the organism has a prediliction to the whole lymphatic system and not to particular classes of glands only. Neither in the animals observed by HOLMES and RAYMOND except four in which HOLMES found the bronchial glands enlarged, fibrous, and to be the seat of abscesses and one in which RAYMOND has reported that the inferior cervical gland showed suppuration and the sublumbar glands were beginning to suppurate, nor in those which came under my observation during the outbreak referred to and subsequently, was there any suppuration or affection of any lymphatic glands other than those concerned in draining the skin areas. The presence of yoke galls and indolent sores on the neck and other wounds in the disease animals that came under the observation of HOLMES and RAYMOND might have been a coincidence. As the large majority of affected animals examined by me both in the outbreak referred to and subsequently had neither yoke galls nor perceptible wounds to which the primary infection could be traced, two issues present themselves for my consideration.

1. What is the possible mode of infection in this disease ?
2. What is the cause of the prediliction to such infection limiting itself only to the superficial glands draining the skin areas of the body, mostly to the precrural and to the prescapular and of the greater prediliction to the precrural in comparison to the prescapular glands ?

In the absence of definite proofs, I propose to map the field of enquiry and to indicate the answer to the first issue by the process of elimination. The only possible modes of infection in a disease are through ingestion, inhalation, or other methods simulating artificial inoculations of the causal agent.

Chart I. Showing the number of animals affected, classified according to the glands involved.

Number of animals affected.



RATIO OF PRECRURAL ABSCESSES TO PRESCAPULAR ABSCESSES TO OTHER ABSCESSES IN THE OUT BREAK.

4. 4:1.6:1.

Key to Chart I.

T. A. Total number of animals affected.
S. P. Animals affected with the precrural gland on one side.
B. P. Animals affected with the precrural gland on both sides.
P. Ps. Animals affected with the precrural and prescapular glands.
Ps. Animals affected with the prescapular gland on one side.
B. Ps. Animals affected with the prescapular gland on both sides.
M. A. Animals with multiple abscesses.
S. I. Animals affected with the superficial inguinal glands.
P. S. Animals affected with the submaxillary lymph glands or with the parotid lymph gland.
I. Animals affected with the ischiatic glands.
D. Total number of deaths (including animals destroyed).

The disease cannot be traced to infection through ingestion either through the medium of food or water or through grazing on an infected soil. If the portal of infection in this disease had been through any one or more of these routes, one should naturally expect lesions in the lymphatic glands of the alimentary tract, long before the superficial glands are affected. No such affection of any of the glands of the alimentary tract has been noticed by me in any of the animals that have died of the disease or has been reported upon by previous workers.

Infection through the second of the routes, *i.e.*, inhalation may also be ruled out of consideration. If this were the portal of infection, the bronchial and mediastinal glands would have been affected long before the superficial glands are involved. But these glands have not shown signs of suppuration or anything unusual even in those animals that showed affection of the lungs and died. The *post-mortem* examination held on them revealed advanced lesions of catarrhal pneumonia, abscesses and infarction in the lungs. HOLMES has stated that even in the majority of animals in which the lungs were filled with abscesses similar to those found in the superficial lymphatic glands, the bronchial glands were not found affected except in the four cases referred to already.

The only possible conclusion, therefore, is that infection in this disease arises through some method or other which simulates artificial inoculation of the causal organism. Such methods of infection usually occur either through any abrasion or wound existing in a healthy animal coming directly or indirectly, in contact, either with the soil or any other material previously infected with the natnral excretions, wounds or abrasions, containing the causal organism, or, through transmission of the causal organism from an infected to a healthy animal by means of insects.

In favour of the first of the above alternatives, it might be argued with great plausibility, that when animals lie down, the lower parts of their abdomen flaps of the flank, dewlaps, generally come in contact with the ground and that animals with abrasions on these parts can easily be infected by previously infected soil, etc. Such infection is likely to involve the various superficial glands.

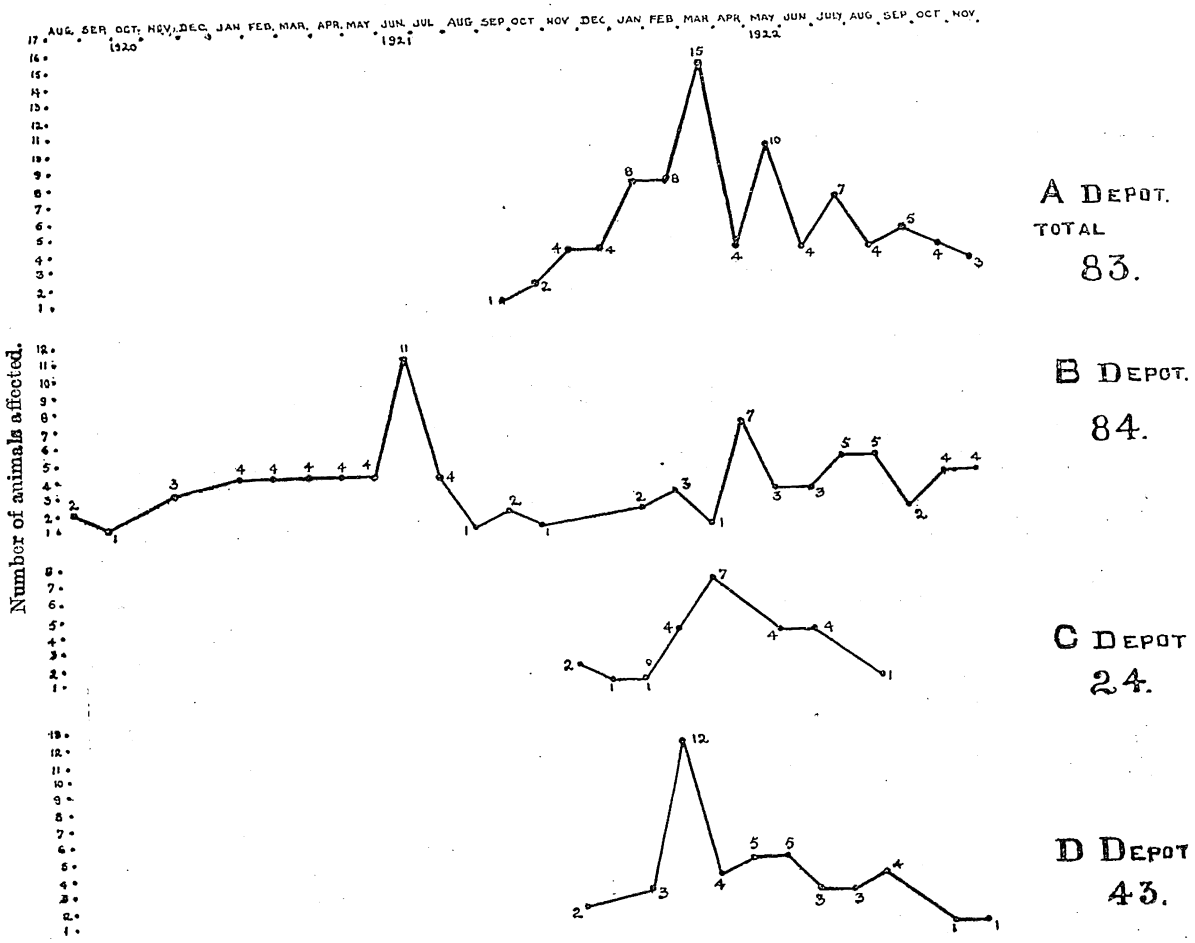
Full consideration has been given by me to the possibility of infection in this manner, but from careful observations made by me during the study of this disease, and for the reasons mentioned below, I consider that the chance of natural infection arising in the above manner, in the normal sequences of events is almost negligible.

1. I have found, in my experience, that the causal organism of the disease is very delicate and the chance of its remaining in the soil and causing infection is very small. Vryburg has also recorded that outside the body, the bacillus rapidly loses its virulence.

2. The sheds in which the animals were kept during the outbreak were always cleaned thoroughly every day and every animal which showed signs of affection of any of the lymphatic glands in the body was isolated long before the gland developed

itself into abscesses. There was, therefore, not the least likelihood of the floor becoming infected with the discharge thereby becoming a source of infection.

Chart II. Showing the number of animals affected in each month.



3. Though animals have been found liable to infection throughout the year, the data furnished in Chart II point to the fact that the disease exhibits a seasonal variation and that the largest number of cases occur in the wake of the breeding season of suctorial insects.

I am therefore led to the conclusion that the infection takes place through the medium of suctorial insects. RAYMOND in his report says that out of the eleven cases sent to his College for treatment, nine cases occurred respectively on the 4th

and 9th April, 24th May, 8th, 20th and 27th June, and 1st, 2nd and 3rd July 1907. HOLMES has reported that the first case occurred in November 1906, no further cases were observed till April 1907 and between that time and the end of December 1907, 85 bullocks were affected. These reports also bear out my observations regarding the seasonal prevalence of the disease. In my examination of the various insects that are likely to be the agents of transmission, I am led to suspect that cattle lice are the more probable agents of dissemination of this disease. Confirmatory experiments are, however, necessary before one definitely incriminates these insects as the actual carriers.

The second of the issues, namely, the reason for the greater prediliction shown by the precrural glands to infection than by the prescapular or by other superficial glands, offers next for consideration.

Prior to the enquiry of the Indian Plague Commission into the prevalence and incidence of Plague in India, it was thought that the reason for the presence of inguinal buboes in the majority of cases in India was that the Indians usually went barefooted and became infected by the plague bacilli getting rubbed into abrasions on their feet. The Plague Commission, however, pointed out that the reason why the groin glands are so frequently affected was simply because they drain the largest skin area and showed that the areas drained by the glands of the neck, axilla, and groin were respectively in the proportion of 1 : 1·8 : 5, while the number of cervical, axillary and inguinal buboes were in the proportion of 1 : 1·3 : 5·8. Further, it is also stated that in communities wearing shoes, the percentage of groin buboes was no less than in those that went barefooted.

Unfortunately, none of the text books on Veterinary Anatomy give any ratio of the extents of the skin areas drained by the several superficial lymphatic glands in cattle. I have worked out as approximately as possible the extent of the areas drained by these glands and their ratio as will be seen from Table 1, approximates very closely in every animal irrespective of its size, breed or age. It may be taken on an average that the areas drained by the precrural, by the prescapular and by other glands taken together are in the ratio of 4·9 : 2·2 : 1 and the data collected during the outbreak investigated by me show that the average ratios of the precrural, prescapular and other glandular abscesses are in the proportion of 4·4 : 1·6 : 1 (Chart I). These figures stand to each other in the same relationship as those arrived at by the Plague Commission and suggest the inference, that the various superficial glandular abscesses on the body are in correlation with the infection of the areas of the skin drained by the respective lymphatic glands.

Inasmuch as the regions inhabited by the lice, which, I think, are the agents of transmission of the disease, are those that are drained chiefly by the precrural and prescapular glands in the order named, it is but natural that these glands are chiefly affected in this disease and that greater prediliction to infection is shown by the precrural glands than by the prescapular glands.

TABLE I.

Showing the approximate extents of the areas of skin drained by the various superficial lymph glands in cattle.

Serial No.	Description of cattle	* Weight in lb.	Area drained by the precrural gland in square inches	Area drained by prescapular gland in square inches	AREA DRAINED BY OTHER LYMPHATIC GLAND IN SQUARE INCHES.				Ratio of columns 4, 5 and 6
					Submaxillary and parotid	Superficial inguinal	Ischiatic	Total of *a*, *b* and *c*	
1	2	3	4	5	*a*	*b*	*c*	6	
1	White bullock (Ranipet)	456	1,792	832	195	48	192	435	4·1 : 1·9 : 1·0
2	Red bullock (Ranipet)	368	1,512	645	180	52	180	412	3·7 : 1·6 : 1·0
3	White bullock (Ongole)	974	2,922	1,472	306	57	214	577	5·1 : 2·6 : 1·0
4	Ditto	823	2,888	1,443	288	60	185	533	5·4 : 2·7 : 1·0
5	Grey bullock (Ranipet)	480	2,146	954	180	64	160	404	5·3 : 2·4 : 1·0
6	White bullock (Alambady)	584	2,276	922	225	64	200	489	4·7 : 1·9 : 1·0
7	White bullock (Kangayam)	569	2,477	1,068	240	64	170	474	5·2 : 2·3 : 1·0
8	Heifer (2½ years)	286	1,372	621	154	39	153	346	4·0 : 1·8 : 1·0
9	Red bullock (Ranipet)	248	1,280	559	132	30	116	278	4·6 : 2·0 : 1·0
10	Calf (8 months)	95	720	300	80	20	48	148	4·0 : 2·0 : 1·0
11	Buffalo (Delhi)	1,161	2,654	948	225	64	150	439	6·0 : 2·2 : 1·0
12	Calf (6 months)	57	493	224	36	16	37	89	5·5 : 2·5 : 1·0
13	Red bullock (Ranipet)	325	1,404	713	121	28	112	261	5·4 : 2·7 : 1·0
14	Bullock (Ongole)	800	2,65[illegible]	1,250	272	66	170	508	5·2 : 2·5 : 1·0
15	White cow (Ranipet)	291	1,427	693	162	39	144	345	4·1 : 2·0 : 1·0
	AVERAGE	..	..	..	..	..	..	..	4·9 : 2·2 : 1·0

* Weight has been calculated according to the formula $\frac{\text{length} \times (\text{girth})^2}{300}$

Etiology.

The causal agent of the disease has been dealt with at length by SHEATHER who, in reviewing the reports of the various workers, has come to the conclusion that the disease is caused by a rod shaped organism. He has described its morphological and cultural characters and also recorded the results of his inoculations in experimental animals with the pus from original lesions as well as with the culture of organism isolated from the pus.

In my experimental inoculations, I have also obtained identically the same results as those got by SHEATHER and I therefore do not propose to record the results of my observations concerning this part of the work at length in this paper except confirming that intraperitonial inoculations in male guinea-pigs either with pus from natural or experimental lesions, or with culture of the organism generally produce suppurative orchitis and encapsuled abscesses in the omentum (Pl. I, Fig. 2), while subcutaneous inoculations in cattle with the same material lead to the involvement of the lymphatic gland nearest to the seat of injection.

Morphology of the organism.

(1) *In Lesions* :—SHEATHER records that it is extremely difficult to detect microscopically the bacilli in lesions. In my experience, detection of the causal organism in lesions entirely depends on the state of the glands from which the smears are made. In those lesions in which suppurating foci have not completely invaded the gland, I have experienced no difficulty in detecting the organism. In smears made from the lesions, taken at a later period, when disorganisation has taken place but not advanced to the state of a caseo-purulent condition, the organism can still be detected after a careful search. Only in lesions where the glandular structure has been completely disorganised into a caseo-purulent condition, it is found impossible to detect the organism in the pus. The stain that I usually empoly for staining the organism in smears of pus is Leishman's stain, and my reason for using this stain is that it not only brings out clearly the morphological characters of the organism but also gives me a good guide by the presence or absence of the staining affinity of the pus cells whether or not it is worth while to continue the search for the organism.

In preparations of smears made from the pus and stained by Leishman's stain, the causal organism is found either singly as a small oval rod or more usually arranged in the form of clumps among pus cells and sometimes scattered in their vicinity. The bacilli show very characteristic bipolar staining with a clear intermediate unstained area and resemble in every respect those of the Pasturella group (Plate III).

(2) *In cultures* :—SHEATHER mentions that growth from the sediment of a 24-hour broth culture is mostly in the form of long filaments which are intricately twisted and coiled together, the filaments not being all alike in appearance and adds that even after 24-hour incubation, involution forms appear, some

of the filaments having rounded swollen ends and some of the bacilli being large and spindle shaped. Preparations made by me from broth culture of the organism presented, however, quite a different picture and revealed chains of the bacilli with distinct bipolar staining, resembling those one gets in broth culture of *Bacillus pestis* (Plate IV, fig. 1).

In preparations made from the surface growth on agar, the bacilli appear as typically small, slender rods, some showing distinct bipolar staining, while others not (Plate IV, fig. 2). Variations in size of these rods exist here and there, and one can see distinctly elongated rods with thickened ends in preparations from cultures incubated for three days.

Very characteristic morphological appearances are exhibited by the organism when cultivated on 3% salt agar. Different remarkable involution forms—coccoid, oval, pyriform and sausage-shaped—are usually found after incubation from 24 hours to 3 days (Plate V and Plate VII, Fig. 1).

The bacillus as recorded by SHEATHER can be stained by any of the simple aniline dyes, but is not "fast" either by the method of Gram, Gram-Weigert or Claudius.

Cultural characters.

I have experienced no difficulty in obtaining primary cultures on agar. On this medium, growth is visible in forty-eight hours and appears as smooth transparent dew drop like colonies which show a great tendency to remain separate, without becoming confluent. In further subcultures, a continuous growth appears along the track of the needle. When the growth is removed for microscopical examination, it is found to be dry and granular, exhibits a tendency to slip away from the needle. It is even difficult to crush it on the slide. I have noticed that this is a constant peculiarity. No luxuriant growth takes place even after incubating the cultures on this medium for a week.

On serum agar, growth is more luxuriant than on ordinary agar, but the cultural characters are the same.

On salt agar, the growth is very faint and scanty and my object in using this medium is with a view to study the characteristic involution forms which form a distinct feature of identification.

In broth the organism grows easily. The growth in this medium is characteristic. The broth remains quite clear and numerous minute powdery deposits are observed to make their appearance from the second day and increase in their number. These deposits are granular in character and appear as if they are adhering to the sides of the flask and with the slightest vibration, they have a tendency to fall down to the bottom of the flask. However, in broth sown from a previous culture of broth, a more or less marked turbidity of the medium appears with a thin surface scum.

No growth is observed on potato.

Milk is not coagulated.

Pathology.

The appearances which the affected gland presents in this disease depend on the state when it is examined. In the early stages, one finds the gland considerably enlarged, tense and indurated. Sections cut from it at this stage, when examined microscopically, reveal a great increase in the bands of its reticulum and a gradual conversion of the glandular tissue into a mass of fibrous tissue, the lymphoid cells becoming more and more scanty as the fibrous tissue is more fully formed until one eventually finds in places only masses of fibrous tissue without even a trace of its original substance (Plate VI, figs. 1 and 2). At this stage, suppurating foci which commence to appear in small areas within the gland begin to extend into the newly formed masses of fibrous tissue, and abscesses of varying sizes are soon formed and distributed over large areas. These areas when examined microscopically reveal pus cells with granular material encapsuled by a fibrous wall (Plate VI, Fig. 1) Endarteritis is very marked and forms one of the special features of the lesions. If the gland is left at this stage without any surgical interference, disorganisation of the entire tissue into a mass of purulent material soon takes place (Plate VII, Fig. 2). Such an abscess when opened is found to contain pus, whitish in colour, of viscid consistency and granular in character.

In some cases, while the disorganisation of the glandular tissue is going on, masses of the causal organism with broken up tissue fragments gain access to the blood stream and set up puriform emboli in the blood-vessels which become finally arrested in the lungs and give rise to catarrhal pneumonia, infarction and pulmonary abscesses which supervene and determine the life of the animal generally long before either the bronchial or the mediastinal glands get affected. Post-mortem examinations held on such animals reveal the lungs to be the only organs showing typical appearance. They present numerous nodules ranging from the size of a big pea to that of a large lime scattered throughout. These nodules are not of a uniform colour. Some are dirty white, while others pure white. When cut into, they are found to contain pus of the same character and consistency as that in the affected glands (Pl. VIII, fig. 1). In some cases, shrinking cavities filled with caseopurulent material simulating those which are found in tubercular lesions are present (Pl. VIII, fig. 2). Sections of the affected portions of the lungs, when examined microscopically, reveal a conditon of catarrhal pneumonia. The bronchial tubes are found filled with catarrhal exudate (Pl. VIII, fig. 3). Their walls show considerable thickening. The epithelium is found proliferating. The alveoli are found in different stages of infiltration, and in some their walls cannot be made out at all, while in others they are just faintly visible. Some of the alveoli are found to be filled with catarrhal cells, while in others croupous exudate forms a prominent feature. Areas of necrotic foci are found in plenty. Leucocytic infiltration surrounding these areas is prominent. In some, the formation of new connective tissue is marked. Infarction due to embolism of the pulmonary artery forms also a predominant feature in the lesions.

Treatment.

Ordinarily, surgical opening of the abscesses, irrigation of the abscess cavities with saline douches and the dressing of them with antiseptic gauzes act as effectively as any other treatment.

However, in such of the cases, in the outbreak referred to, as were not amenable to the above line of treatment, a vaccine was prepared and used.

The organism was grown in broth for six weeks, to which was added a 72-hours' broth culture of the same organism, in the proportion of 1 : 4. The mixture was exposed to 58°C for half an hour and carbolic acid was subsequently added in the proportion of ·5 per cent. The dose of the vaccine used varied from 10 to 40 c. c. injected subcutaneously. The number of injections and the intervals between each injection depended on each case treated.

In those cases which were considered from the nature of the lesions exhibited by the animals to be likely to give trouble, vaccine was used from the very commencement of the local treatment ; while in others, only when it was found that the local treatment was ineffective, vaccine treatment was commenced. In addition to the treatment of animals at the hospital, vaccine was also issued to the Chief Superintendent in charge of the Corporation depots to be tried on selected cases not responding to local treatment. The report furnished by him to the Principal of the Madras Veterinary College in the form of two statements is subjoined (Tables II and III).

TABLE II.

Showing list of animals subjected to multiple abscess vaccine treatment in D. Depot—Harris Road.

Serial No.	Bullock No.	Date of operation	No. of abscesses	DATE OF INOCULATION			Results	REMARKS
				1st	2nd	3rd		
1	D. 40	5th January 1922 15th March 1922	2	28-4-22	2-5-22	7-5-22	Discharged on 27th May 1922.	
2	D. 4	1st February 1922 28th April 1922	3	Do.	Do.	Do.	Ditto.	
3	D. 127	1st February 1922 28th April 1922	10	Do.	Do.	Do.	Discharged on 7th June 1922.	
4	D. 36	14th February 1922 15th March 1922	1	Do.	Do.	Do.	Discharged on 27th May 1922.	
5	D. 3	10th February 1922 15th March 1922	50	Do.	Do.	Do.	Died on 10th May 1922.	
6	D. 69	31st March 1922	2	Do.	Do.	Do.	Condemned and sold	Developed lameness in both fore.
7	D. 99	Ditto. 2nd May 1922	7	Do.	Do.	Do.	Discharged on 15th June 1922.	
8	D. 89	28th April 1922	2	Do.	Do.	Do.	Discharged on 27th May 1922.	
9	D. 104	Ditto. 23rd May 1922	2	Do.	Do.	Do.	....	Still under treatment.
10	D. 138	28th April 1922	8	Do.	Do.	Do.	Died on 18th June 1922.	

TABLE III.

Showing the bullocks injected with multiple abscess vaccine and the results.

Serial No.	Bullocks No.	No. of abscesses	No. of injections	Dates of injections	Date of operation	Result	REMARKS
1	A. 37	7	4	26th March 1922 30th March 1922 5th April 1922 9th April 1922	7th March 1922	Discharged on 8th April 1922.	
2	A. 128	26	3	26th March 1922 30th March 1922 4th April 1922	1st February 1922	Died on 9th April 1922	8 more abscesses formed after injection.
3	A. 65	5	4	26th March 1922 30th March 1922 15th April 1922 9th April 1922	7th March 1922	..	Developed one on off flanklosing condition and coughing.
4	A. 87	17	4	26th March 1922 30th March 1922 4th April 1922 9th April 1922	Ditto	Discharged on 14th April 1922.	
5	A. 17	12	1	26th March 1922	1st March 1922	Died on 28th March 1922.	
6	A. 27	8	4	Ditto. 30th March 1922 4th April 1922 9th April 1922	15th February 1922	Died on 13th April 1922.	
7	A. 80	9	4	Ditto	1st February 1922	..	Abscess formed in front of the one already operated.

TABLE III.

Showing the bullocks injected with multiple abscess vaccine and the results—contd.

Serial No.	Bullocks No.	No. of abscesses	No. of injections	Dates of injections	Date of operation	Result	REMARKS
8	A. 8	2	4	9th April 1922	1st October 1921	..	One developed in front of the one already operated. Abscess increasing in size and furrowing—no tendency to heal.
9	B. 42	12	4	26th March 1922 30th March 1922 2nd April 1922 7th April 1922	29th January 1922	Died on 13th April 1922.	Two more developed—Coughing and heavy breathing.
10	B.-169	4	4	Ditto	19th February 1922	Discharged on 21st April 1922.	
11	A. 96	10	4	26th March 1922 30th March 1922 5th April 1922 19th April 1922	22nd January 1922	Died on 22nd April 1922.	
12	A. 10	3	4	30th March 1922 4th April 1922 7th April 1922 9th April 1922	21st November 1921	Died on 10th May 1922.	Big abscess formed underneath the ones operated with fibrous growth. Operated again on 27th April 1922. Developed heavy and laboured breathing and cough on 8th May 1922.
13	A. 5	2	3	30th March 1922 4th April 1922 9th April 1922	7th March 1922	Discharged on 14th April 1922.	But pus formed in the healed one: one new one formed at the angle of off-jaw and below ear on the same side.
14	A. 47	7	3	Ditto	19th February 1922	Discharged on 10th April 1922.	

Abstract :—6 died, 3 yet under treatment, 4 discharged, 1 developed after discharge.

A concise description of each of the cases treated at the College hospital with the vaccine is given below.

No. 1. Case No. 28/1921.

Red and black bullock B-16 admitted on 20-v-21 with abscesses on the left flank and scrotum. Vaccine treatment was commenced from 21-v-21. Four injections of the vaccine were given :—

10 c. c.	on 21-v-21
20 "	" 23-v-21
30 "	" 25-v-21
30 "	" 29-v-21

The abscesses were opened on 29-v-21 and the animal was cured and fit for discharge on 27-vi-21.

No. 2. Case No. 29/1921.

Grey bullock B-32 admitted on 20-v-21, with abscesses on the face ; the gland affected was the left parotid lymph gland with small abscesses near and around the primary one. Vaccine treatment was commenced from 27-v-21, and three injections were given :—

10 c. c.	on 27-v-21
10 "	" 29-v-21
20 "	" 3-vi-21

The abscesses healed by 24-vii-21, though the animal was detained for another complaint till 9-ix-21.

No. 3. Case No. 30/1921.

White bullock B-155 admitted on 20-v-21 with the left precrural gland hard and indurated ; vaccine treatment was commenced from 21-v-21 and four injections were given :—

10 c. c.	on 21-v-21
20 "	" 23-v-21
30 "	" 25-v-21
30 "	" 29-v-21

The abscesses were opened on 30-v-21 and the animal was cured and fit for discharge on 18-vi-21.

No. 4. Case No. 31/1921.

White bullock B-44 admitted on 21-v-21 with a number of abscesses ; both the precrural and prescapular glands were affected ; the animal was poor in condition with overgrown hoofs. Four injections of the vaccine were given :—

10 c. c.	on 27-v-21
20 "	" 29-v-21
20 "	" 3-vi-21
30 "	" 8-vi-21

As the animal did not improve in condition and showed affection of the lungs, it was recommended to be destroyed.

No. 5. Case No. 39/1921.

Grey bullock C-36 admitted on 4-vi-21 with abscesses at the parotid region. The left parotid gland was found hard and indurated with a number of small abscesses in and around it. As the animal did not get any relief with the local treatment, vaccine treatment was commenced from 16-xi-21. Three injections were given :—

30 c. c.	on 16-xi-21
30 "	" 30-xi-21
30 "	" 8-xii-21

The abscesses healed by 13-ii-22. As there was still left a hard tumour with a fibrous thickening, it was decided to remove it, which was done on 15-ii-22, and the animal was cured and discharged on 30-v-22.

No. 6. Case No. 48/1921.

Light red bullock B-125 admitted on 18-vi-21 with abscesses on the left flank. As the local treatment afforded no relief to the animal inasmuch as more than 10 abscesses formed within a course of about five months, and as the condition of the animal began to be affected very much, vaccine treatment was commenced from 16-xi-21. Three injections were given :—

30 c. c.	on 16-xi-21
30 "	" 30-xi-21
30 "	" 8-xii-21

The animal was cured and discharged on 6th June 1922.

No. 7. Case No. 56/1921.

Grey bullock C-107 admitted on 28-vi-21. At the time of its admission a few small abscesses in the form of buds were found on the region of the left side of the neck. The abscesses were opened and the local treatment was adopted until 6-v-21. As more abscesses extending along the region of the neck began to develop, and the animal was also losing condition, vaccine treatment was resorted to from 16-viii-21. The animal received eleven injections of the vaccine as detailed below :—

10 c.c.	on 16-viii-21
10 "	" 19-viii-21
10 "	" 21-viii-21
30 "	" 23-ix-21
20 "	" 26-ix-21
20 "	" 27-ix-21
30 "	" 23-x-21
30 "	" 10-xi-21
30 "	" 16-xi-21
30 "	" 30-xi-21
30 "	" 8-xii-21

The animal with the commencement of the vaccine treatment began to improve in condition and was fit for discharge in its best of health on 3rd January, 1922. During its stay in the hospital as many as 33 abscesses developed.

No. 8. Case No. 67/1921.

White bullock C-98 admitted on 21-vii-21 with an abscess involving the right precrural gland. This animal was given every method of local treatment till 16-xi-21, when as more abscesses began to develop and the animal began to lose condition, vaccine treatment was commenced and three injections were given :—

30 c. c.	on 16-xi-21
30 "	" 30-xi-21
30 "	" 8-xii-21

The animal was cured and discharged on 20th April, 1922.

No. 9. Case No. 97/1921.

White bullock B-47 admitted on 21-ix-21. Soon after its admission, the animal showed symptoms of affection of the lungs and received symptomatic treatment. Vaccine treatment was commenced from 5-xi-21 and two injections were given :—

30 c. c.	on 5-xi-21
30 "	" 16-xi-21

The treatment gave the animal no relief and the animal died on 11-xii-21.

No. 10. Case No. 98/1921.

Black bullock B-109 admitted on 21-ix-21. The gland affected was the left precrural gland, which was hard and indurated. Three injections of the vaccine were given :—

10 c. c.	on 23-ix-21
20 "	" 26-ix-21
20 "	" 29-ix-21

The animal was cured and discharged on 17-x-21.

No. 11. Case No. 116/1921.

White bullock B-40 admitted on 26-x-21 with a big abscess involving theright prescapular gland and small abscesses around it. The usual local treatment was

given until 5-xi-21, but as the animal was found to develop more abscesses and its condition began to be affected, vaccine treatment was commenced from 5-xi-21. Three injections were given :—

30 c. c.	on 5-xi-21
30 "	" 16-xi-21
30 "	" 19-xi-21

The animal was cured and discharged on 9th February, 1922.

No. 12. Case No. 118/1921.

White bullock D-9 admitted on 1-xi-21 with a precrural abscess on the left flank. This animal was given the usual treatment till 16-xi-21. As more abscesses began to develop along the sternum and the chest, vaccine treatment was commenced from 16-xi-21. Three injections were given :—

30 c. c.	on 16-xi-21
30 "	" 30-xi-21
30 "	" 8-xii-21

The animal was cured and discharged on 6th January, 1922.

No. 13. Case No. 133/1921.

White bullock C-1 admitted on 18-xi-21. This animal had seven abscesses and both the precrural glands were affected. Vaccine treatment was commenced from 25-xi-21. Three injections were given :—

20 c. c.	on 25-xi-21
20 "	" 30-xi-21
30 "	" 8-xii-21

The animal was cured and discharged on 5-iii-22.

No. 14. Case No. 138/1921.

Red and white bullock D-8 admitted on 23-xi-21 with an indurated abscess involving the right precrural gland and three other smaller abscesses around it. Vaccine treatment was commenced from 25-xi-21. Three injections were given :—

20 c. c.	on 25-xi-21
20 "	,, 30-xi-21
30 "	,, 8-xii-21

The animal showed no relief and died on 7th February, 1922.

No. 15. Case No. 139/1921.

Red bullock D-37 admitted on 23-xi-21 with multiple abscesses. Vaccine treatment was commenced from 25-xi-21. Three injections were given :—

20 c. c.	on 25-xi-21
20 "	" 30-xi-21
30 "	" 8-xii-21

The animal was cured and discharged on 6th January, 1922.

No. 16. Case No. 193/1922.

White bullock C-148 admitted on 2-iii-22 with abscesses involving the right thigh and both the precrural glands. The usual treatment was given till July, but as the animal was losing condition and more abscesses began to form, it was transferred to me for treatment with the vaccine. The animal received four injections commencing from 16-viii-22 :—

20 c. c.	on 16-viii-22
20 "	" 22-viii-22
40 "	" 31-viii-22
40 "	" 5-ix-22

The animal was cured and discharged on 10-ix-22.

No. 17. Case No. 194/1922.

White bullock A-84 admitted on 3-iii-22 with a precrural abscess. The usual treatment was given until 18-vi-22 when tertiary abscesses began to form all over the body. Concurrent with these abscesses, the animal began to show lung affection and at this stage on 22-viii-22, vaccine treatment was commenced and four injections of the vaccine were given :—

20 c. c.	on 22-viii-22
40 "	" 31-viii-22
40 "	" 5-ix-22
20 "	" 11-ix-22

The treatment afforded no relief and the animal died on 27-ix-22.

Conclusions.

1. The various abscesses found in the animals affected with this disease are limited mostly to those lymphatic glands that are concerned in draining the skin areas of the body.

2. Of these glands, the precrural glands are affected most, to a less degree the prescapular, and to a still less degree the other glands, the affection being in correlation with the infection of the skin areas drained by the respective glands. In the writer's opinion, cattle lice appear to be the probable transmitting agents of the infection.

3. In some cases owing to the disorganisation of the glandular tissue, puriform emboli may be set up in the blood-vessels resulting in affection of the lungs.

4. The causative agent resembles the one described by SHEATHER. This can be demonstrated in smears of pus from natural as well as experimental lesions taken from the affected glands before they have undergone complete caseation.

5. The organism shows extensive pleomorphism on culture media.

6. Intraperitoneal inoculation of male guinea-pigs either with pus from natural lesions or with culture of the organism generally produces orchitis and encapsuled omental abscesses in guinea-pigs.

7. Sections of affected glands reveal in early stages extensive formation of new connective tissue with suppurating foci.

8. When the lungs become involved they are found studded with nodules which contain pus similar in character to that in the affected glands. Sections from affected lungs reveal catarrhal pneumonia, infarction and abscesses.

9. In animals in which the lungs are involved, neither the bronchial nor the mediastinal glands generally show any affection.

10. Prognosis is usually favourable provided the lungs are not affected; when they are affected it is unfavourable.

11. Ordinarily, surgical opening of the abscesses, irrigation of the abscess cavities with saline douches and dressing them with antiseptic gauzes, act as effectively as any other treatment.

12. The results of treatment with a vaccine prepared from broth culture of the organism and used in such of the cases as were not amenable to the treatment indicated above, appear to show that the vaccine has a curative effect.

I am very much indebted to MR. AITCHISON for the uniform encouragement and help which he extended to me during the long period of my investigation of this disease.

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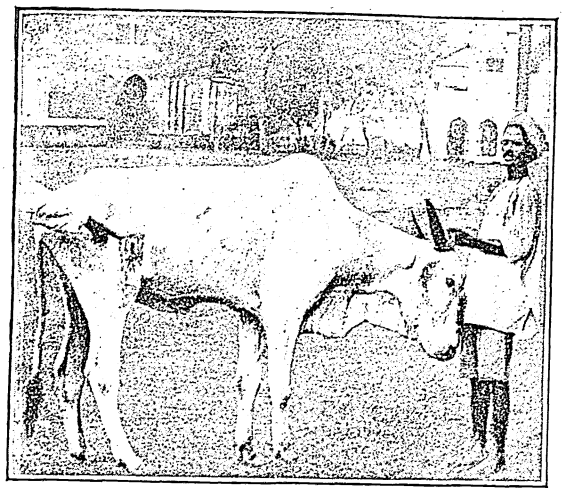
PLATE 1.

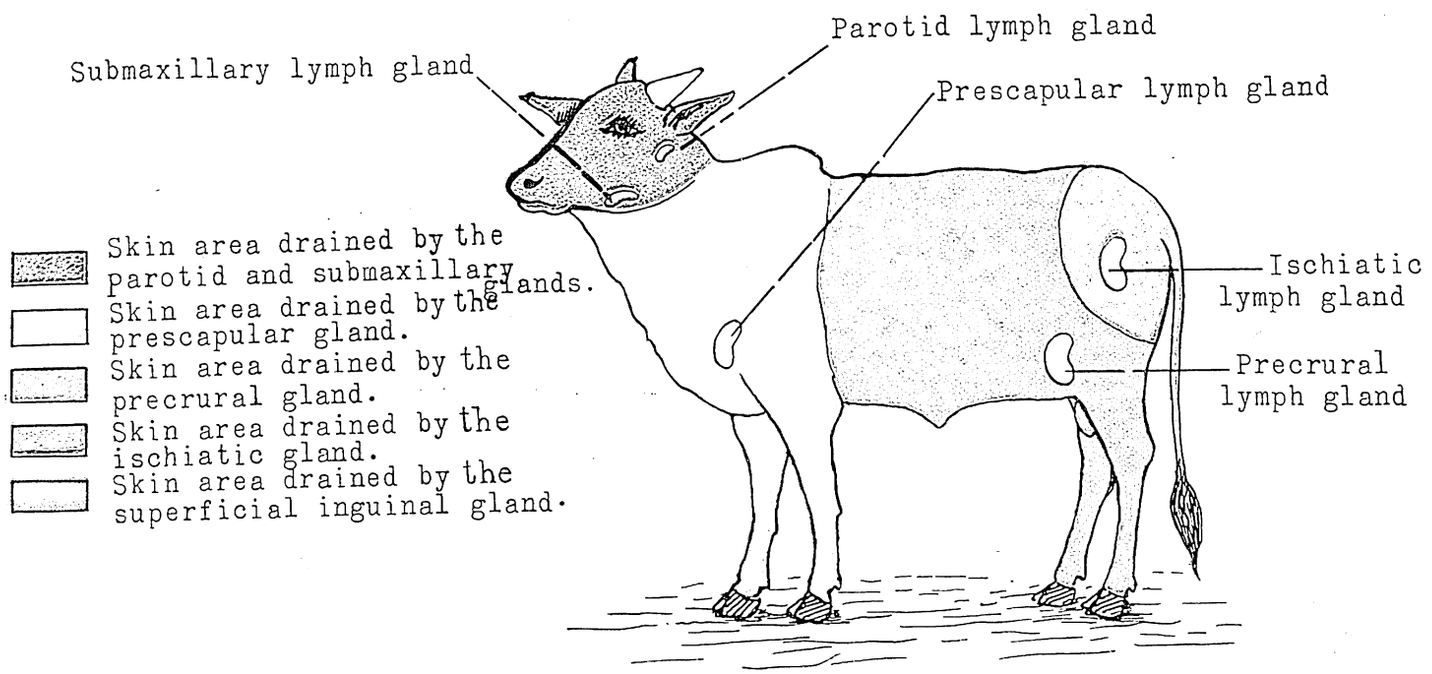


1. Bovine Lymphangitis. A bullock in an advanced state of the disease.

A

B

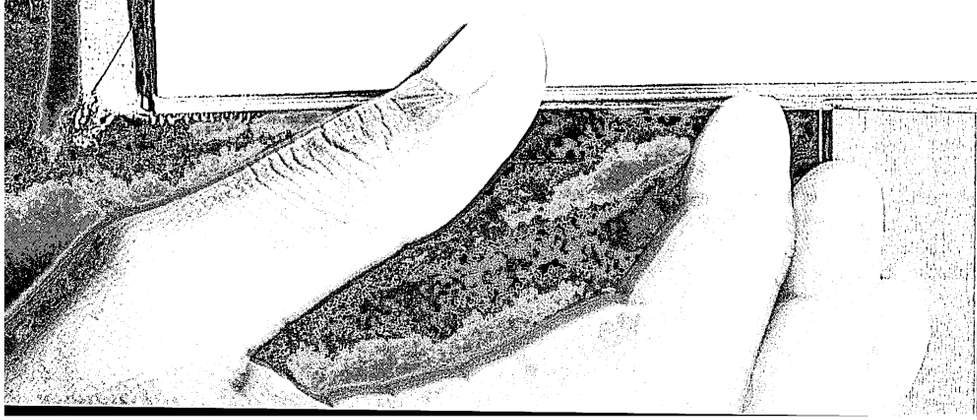
2, A. A guinea-pig showing orchitis as a result of intraperitoneal injection with broth culture of the organism of bovine lymphangitis.
B. A male guinea-pig (normal).

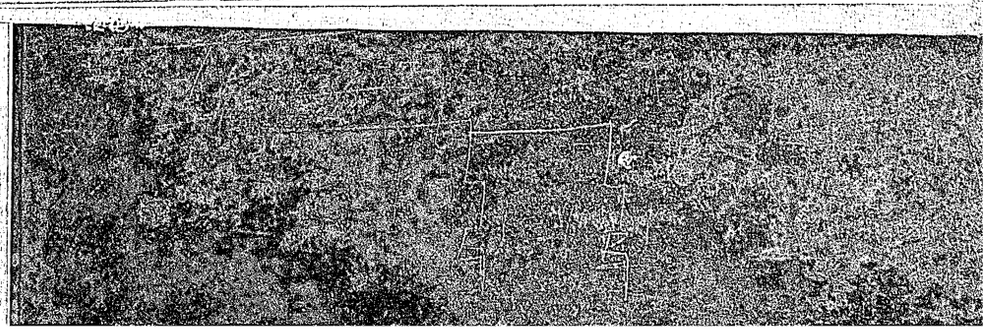


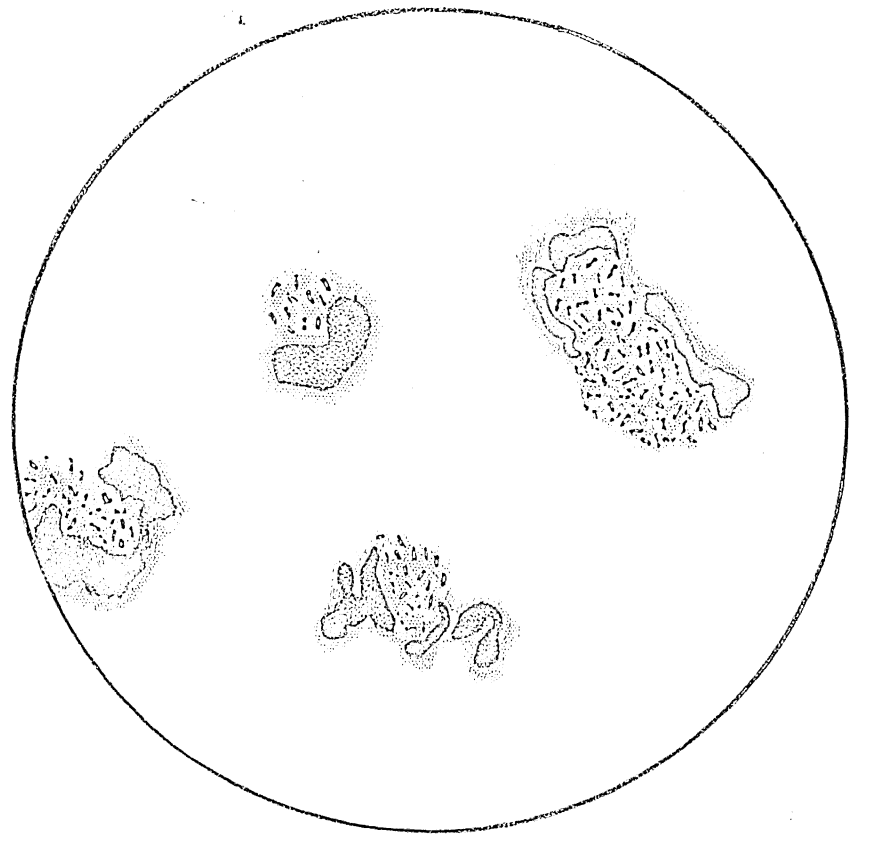
N. B.—The correct position of the superficial inguinal glands could not be shown in the diagram. They are found in the bull below the prepubic tendon and in the narrow interfemoral space and lie in the mass of fat about the neck of the scrotum and behind the spermatic cord.

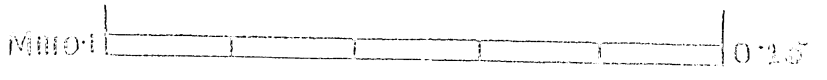
Diagram showing the approximate extents of skin areas drained by the different lymph glands in the bull.

PLATE II.









Organism of bovine lymphangitis in a smear preparation from a precrural abscess (natural lesion) in a bullock. Drawn to scale with camera lucida, 1-12th objective and No. 4 eye-piece. Stained with Leishman's stain.

PLATE IV.

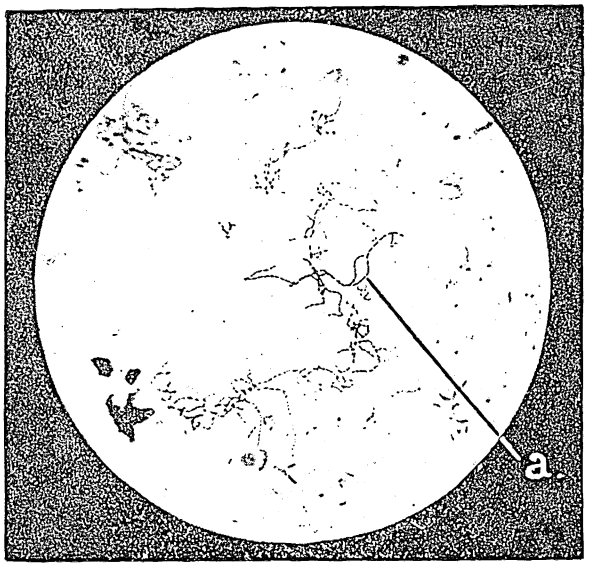


Fig. 1. *a.* Organism of bovine lymphangitis from a 48 hours' broth culture, showing chain forms.

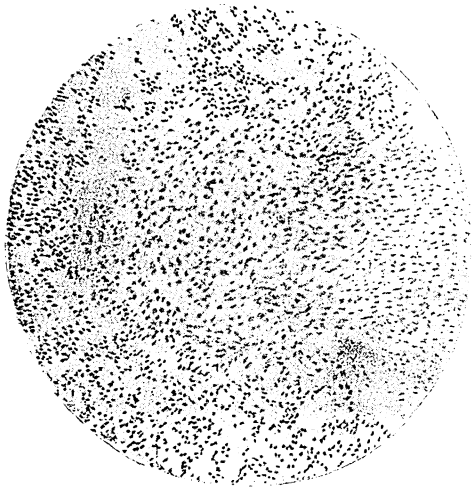


Fig. 2. Organism of bovine lymphangitis from a 48 hours' agar culture.

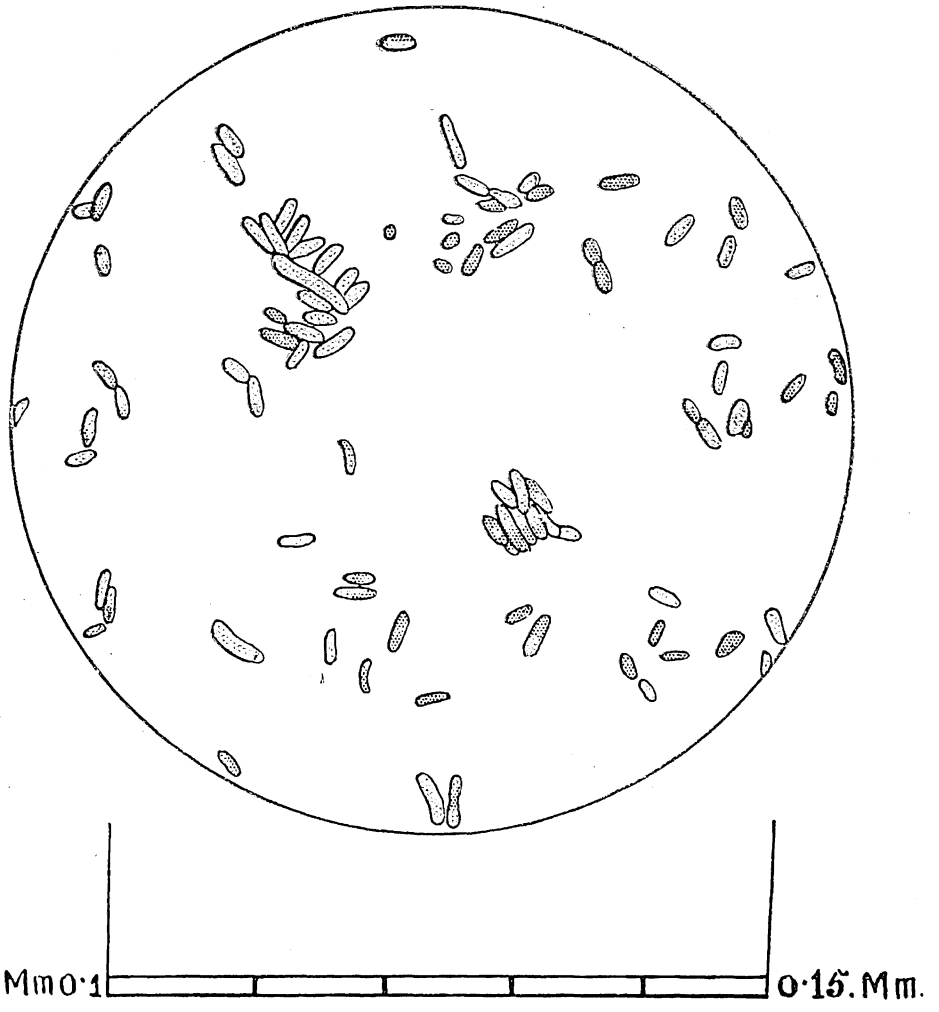
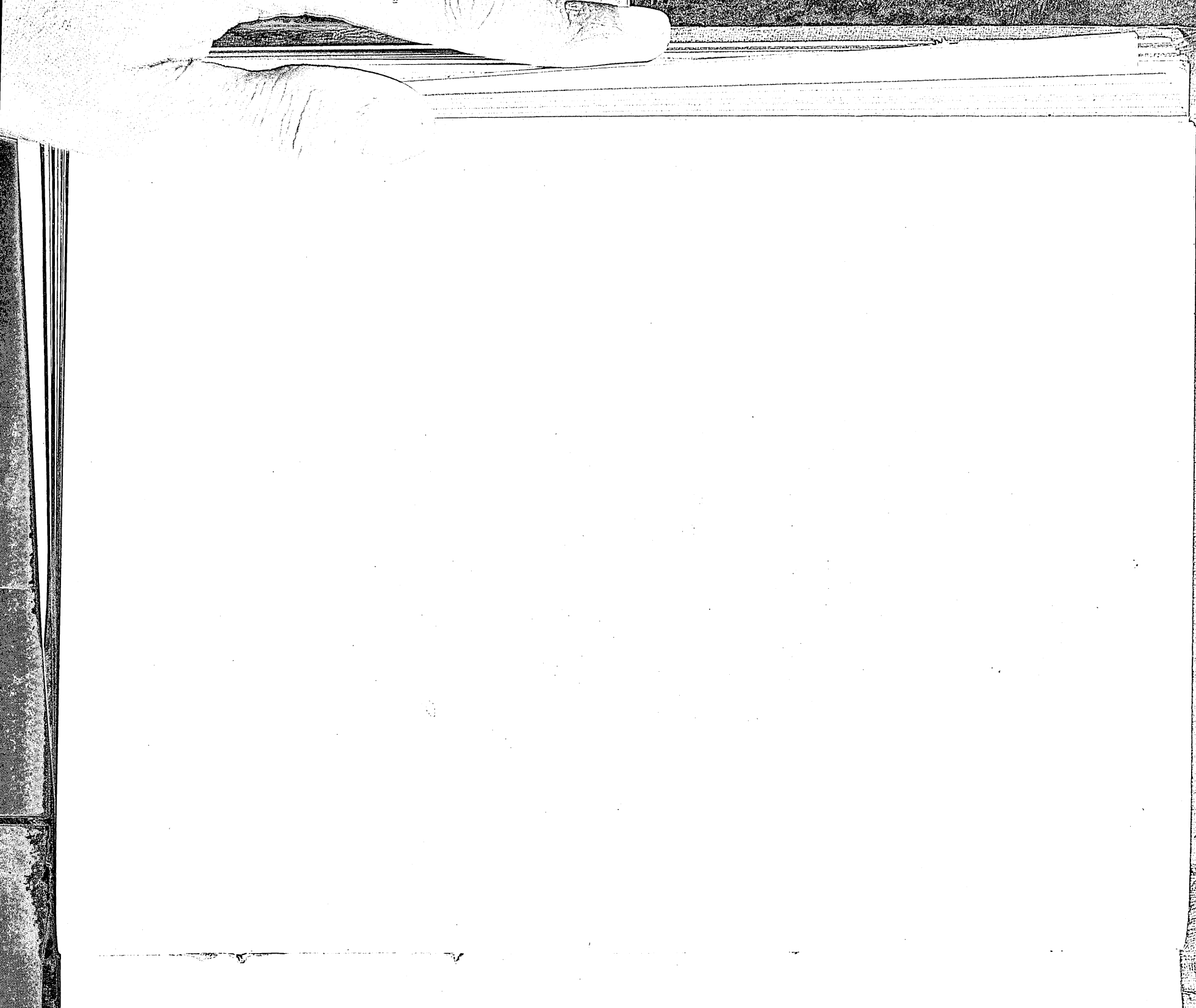


PLATE V.

Organism of bovine lymphangitis from a 48 hours' salt agar, culture, showing involution forms.
Drawn to scale with camera lucida 1-12th objective and No. 4 eye-piece. Stained with carbol-fuchsin.



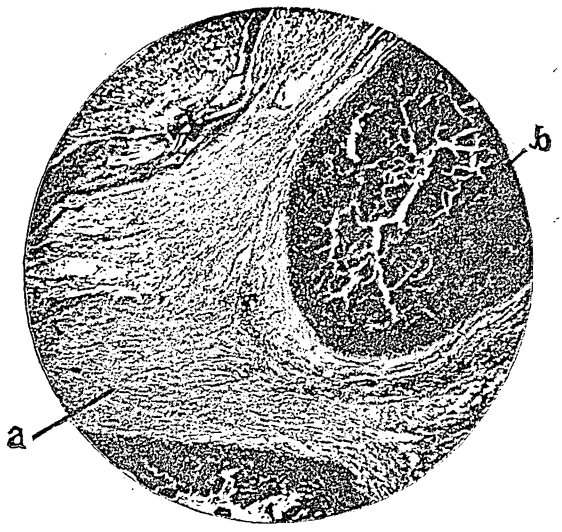


Fig. 1. Bovine lymphangitis. Section of precrural lymph gland from a bullock.
(*a*) Glandular srtucture transformed into a fibrous mass without any trace of its original substance.
(*b*) Suppurating area in the gland occupied by pus cells with granular material encapsuled by a fibrous wall.

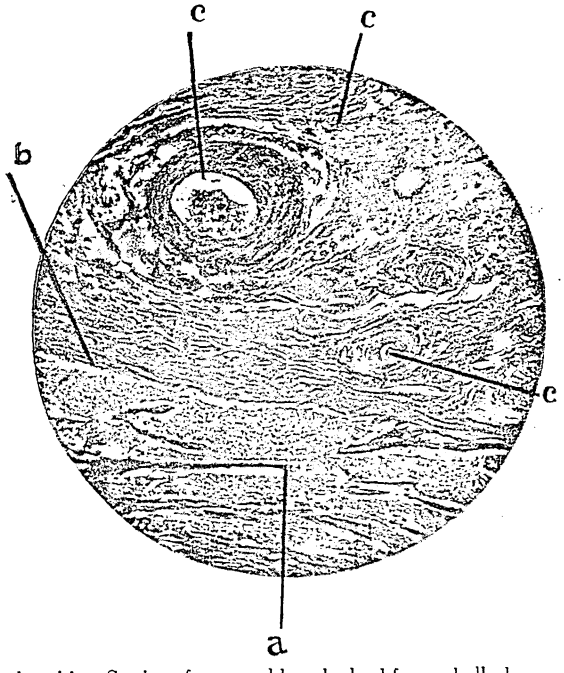
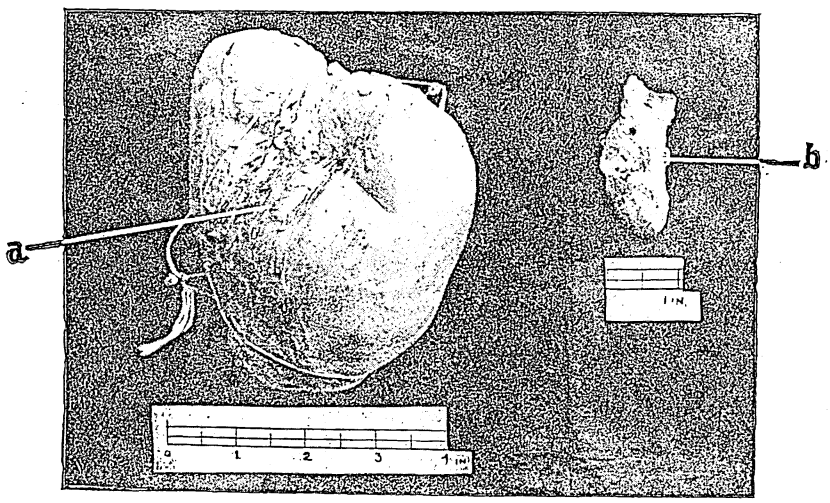
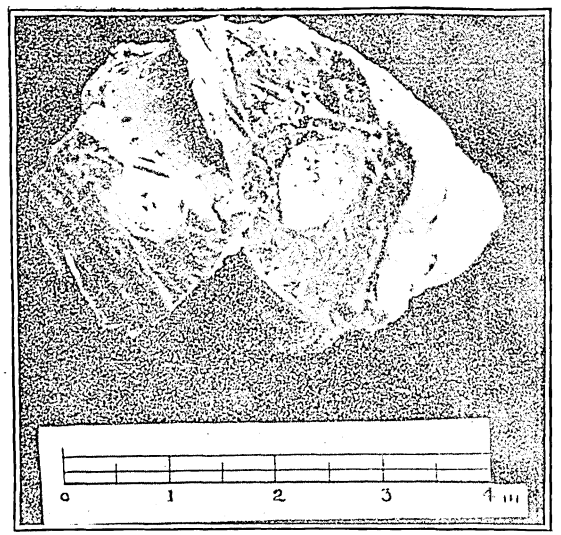


Fig. 2. Bovine lymphangitis. Section of precrural lymph gland from a bullock.
(*a*) Glandular structure which has not undergone any alteration.
(*b*) Areas in which glandular structure has undergone fibrous formations.
(*c*) Blood-vessels showing thickened walls. In one the lumen is occupied by an embolus.

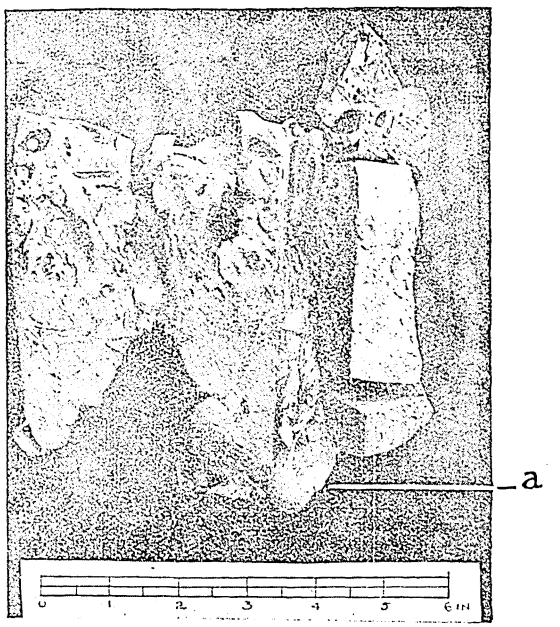
1. Organism of bovine lymphangitis from a salt agar culture 3 days' old showing involution forms..



2 Bovine lymphangitis.
(*a*) Parotid lymph gland from a bullock, considerably enlarged with purulent material inside..
(*b*) Normal parotid lymph gland from a bullock.



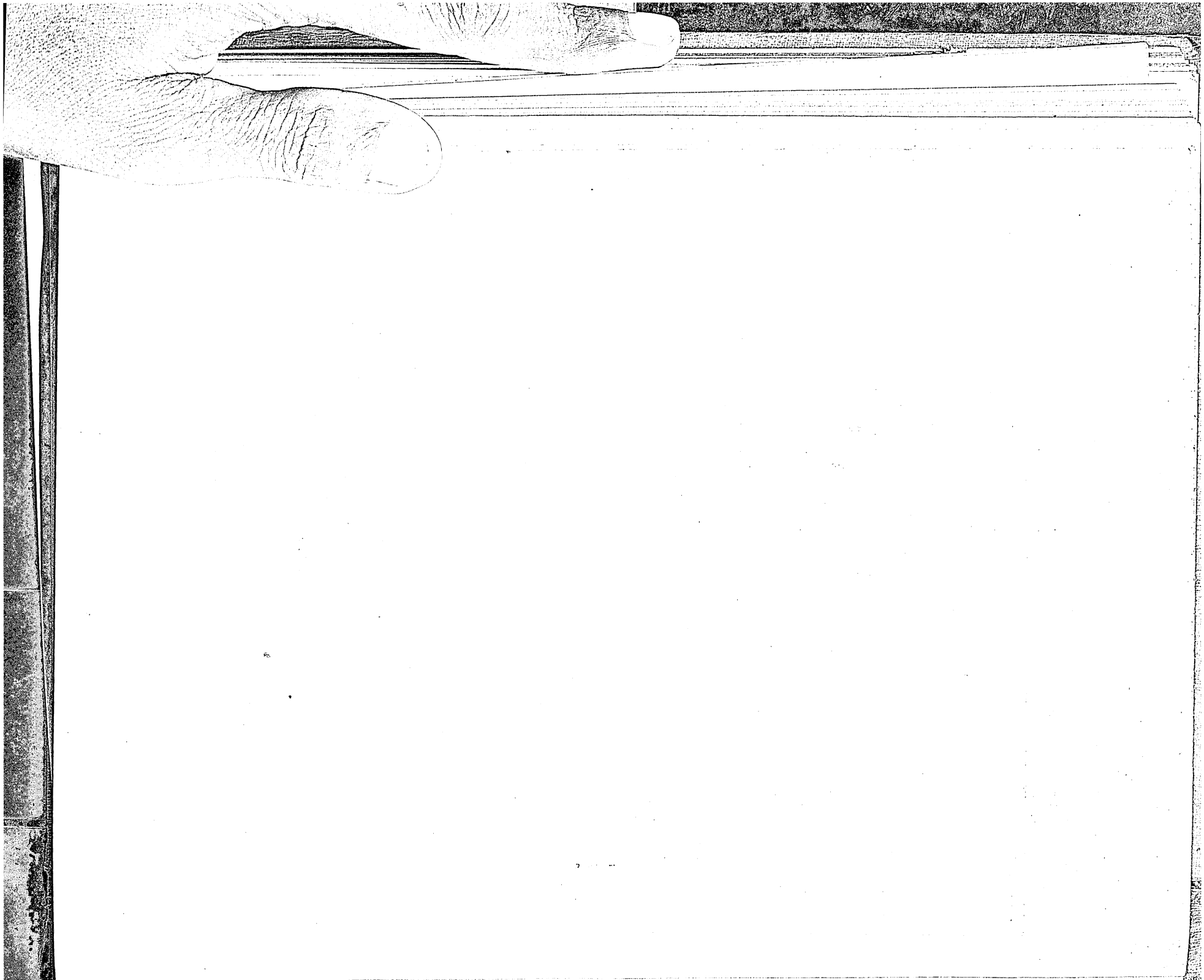
1. Bovine lymphangitis. Lungs showing suppurating foci in the centre.



2. Bovine lymphangitis. Lungs showing shrinking cavities, filled with pus.
(*a*) Bronchial gland not affected.

3. Bovine lymphangitis. Section of lungs from a bullock showing catarrhal pneumonia.

PLATE VIII.



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Second Superintendent, Civil Veterinary Department, Central Provinces, India

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TRYPANBLUE AND CERTAIN DITHIO-ANILINE DERIVATIVES: THEIR EFFICACY IN THE TREATMENT OF PIROPLASMOSIS AND OTHER AFFECTIONS IN THE CENTRAL PROVINCES.

BY

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Introduction.

Piroplasmosis, or tick-fever, is the most widespread infection of animals in the Central Provinces. The ubiquity of the infection may be adjudged by the fact that blood smears taken from all animals accessible in a number of villages, chosen at random, disclosed on examination piroplasms of various kinds in the proportion of 75 to 80 per cent. of the specimens. Further, in the great majority of the infected animals, symptoms that would lead a clinical observer to suspect infection with piroplasms were not detected. Nevertheless, the clinical state of most of the animals was indicative of ill-health, with anæmia, general debility and loss of condition amounting to extreme emaciation in three to four per cent. of the cattle population in the villages, as the most noticeable symptoms.

In the course of these examinations, it was impracticable to undertake a minute laboratory examination upon the specific nature of the piroplasms. So far as we know at present, mainly from the recent surveys undertaken by the Muktesar Institute, the cattle of India are commonly infected with two species of piroplasms, namely :—

(*a*) *Piroplasma* (*Babesia*) *bigeminum*, the cause of tropical redwater, or Texas fever. Infection with this parasite is very widespread in India, and indigenous cattle are generally held to be immune from serious ill-effects as the result of infection with it. Their immunity is explained on the assumption that the great majority become infected when they are very young, from the bites of ticks, at a stage in their lifetime when it is known that cattle are relatively resistant. Having recovered from the very slight or inappreciable attack produced by this infection, they are subsequently immune from, at any rate,

typical attacks of redwater, unless, by chance, they happen to contract infection with some other disease, such as rinderpest, which lowers their resistance to the piroplasms and allows these parasites to develop again to the status of pathogenic organisms. Attacks of redwater are, nevertheless, observed from time to time in Indian cattle, and these attacks are generally explained on the assumption that circumstances have permitted the cattle to escape anterior infection, when their natural resistance had not commenced to wane. It is our belief, however, from clinical observation of cattle in villages and from the evidence that has been brought to our notice concerning the efficacy of trypanblue and other remedies, which have a specific effect against this type of piroplasm, in producing a very marked amelioration in the condition of the animals, that much of the debility and anaemia observed in Indian cattle is attributable to the persistent effects of the piroplasms.

(*b*) *Theileria mutans*. This small piroplasm is now known to be found almost everywhere among Indian cattle, and it is generally held that it sets up no clinical symptoms. With the relatively heavy infection sometimes observed, it is, however, difficult to believe that the presence of the organisms can be wholly without effect upon the animals. It has been reported that very rarely sporadic deaths may be caused by infection which for some unexplained reason has become suddenly highly virulent, and that the changes seen in the carcase after death resemble those of East Coast fever. This phenomenon has been further reported to assume special significance in imported cattle. This type of infection is stated not to yield to the effects of trypanblue.

The piroplasmosis of the canine population of India is also known to be caused by two different species of parasites :—

(*a*) *Piroplasma* (*Babesia*) *canis*, the cause of the so-called malignant jaundice. Infection with this piroplasm has long been known to yield in a remarkable manner to trypanblue.

(*b*) *Piroplasma gibsoni*. The affection caused by this much smaller piroplasm differs clinically from that caused by *P. canis*, in that it is usually more prolonged in its effects and the symptoms are generally those of a progressive anaemia, with a frequent tendency to relapses at prolonged intervals. It is known to be surprisingly common now in many parts of India. It does not respond, it would seem, to trypanblue, but good results may be obtained by repeated treatment with certain arsenical preparations, notably tryparsamide.

The dipping of cattle, at regular intervals, in arsenical baths, is now practised on an enormous scale in many parts of the world as a means of destroying ticks, to prevent the development in the cattle of the infections transmitted by them. In

the Central Provinces, the proper dipping of cattle is impracticable for many reasons. The cattle owner is not sufficiently educated to appreciate the necessity for the institution of measures of this kind, and would resent and evade them if they were introduced. The veterinary staff is not strong enough to undertake the proper supervision of the dipping. Added to these reasons, there is a technical reason of paramount importance why it would be altogether unwise to resort to dipping measures in small circumscribed areas, where the circumstances might otherwise permit of their institution. Dipping to be effective in the prevention of piroplasm infections must be practised in a thorough manner within the widest possible geographical limits. Short of this, there will remain some cattle that will carry the piroplasms, which will again infect the ticks of their neighbourhood. It is then likely that the properly dipped cattle will contract infection from these ticks when they have so far advanced in life that they have lost their early immunity towards the disastrous results provoked by the piroplasms. Except, therefore, where cattle are grossly attacked by immense numbers of ticks and dipping is practised merely to reduce their numbers, so as to prevent rapid loss of condition caused by large extraction of blood, it is not recommended for territories circumstanced like the Central Provinces.

It seemed to the writer, therefore, that a line of control meriting trial would be to treat animals therapeutically with drugs known to be effective against certain species of piroplasms on as large a scale as possible wherever the veterinary staff saw good reason to assume that there was ill health of the kind attributable to blood parasites. It will be appreciated by the reader that proper control of the results was not practicable, for the reason that the subordinate veterinary staffs, to whom the actual treatment necessarily had to be entrusted, were not armed with the means for carrying out precise investigations upon the actual presence of piroplasm infection in the treated animals, or of differentiating the species of piroplasms if they should discover them. Furthermore, any beneficial effect observed after the treatment might be attributable in no small degree to its action upon disease processes other than that set up by the piroplasms specifically susceptible to the action of the treatment. The employment of drugs in these circumstances must be regarded as very largely in the nature of empirical therapeutics, which, although the term senses an unscientific implication, is, in reality, the basis of most endeavours in human and veterinary medicine. It has a rational basis, however, in so far as it is a treatment aimed at a certain form of infection known to be very widespread in the Central Provinces, which, again, is known by exhaustive experience to yield in a remarkable manner to the treatment.

In 1921, the writer approached the Veterinary Adviser to Government, Central Provinces, (Mr. C. W. Wilson, M.R.C.V.S.) with proposals for undertaking treatment in this manner and for permission to execute them on as large a scale as possible. The writer is much obliged to him for granting readily his consent, and for his encouragement in prosecuting the work.

Trypanblue.

1. *Preparation of solution.* The brand of trypanblue recommended is the *trypanblau* manufactured by the German firm, Merck, of Darmstadt. The drug supplied by this firm is eminently superior in properties to the products the author has been able to secure elsewhere. In the years 1921 and 1922, supplies were obtained from a British firm for trial, and they were found to be less soluble than the German product and frequently became gelatinous in solution on cooling.

The drug, which is a blue dye, of the aniline dye series, is made up in two per cent solution in water. The powder is weighed out into a mortar, and finely triturated with a small amount of cold water into a paste ; more water is then gradually added until the dye enters completely into solution, which is then made up to the desired bulk. The solution is next passed through ordinary filter paper, and the filtrate collected in a wide-mouthed flask, which is afterwards placed in an autoclave maintained at 120°C for 20 minutes. When the solution in the flask has cooled, it is distributed into sterile bottles, which are then carefully sealed and despatched to the District Veterinary Assistant Surgeon staff as required.

2. *Dose.* The dose administered is 40 c.c. for horses and cattle, and 5 to 6 c.c. for dogs. These doses may appear to be rather low. The cattle of the Central Provinces, however, are generally of a small type, and as the drug is usually employed upon animals that are much sunk in condition, it has been considered prudent to recommend for adoption a dose rate somewhat lower than what is sometimes recommended in treatment. Larger doses were sometimes followed by symptoms of dyspnoea and temporary collapse, and although these symptoms passed off without untoward incident to the animal itself, they caused alarm in the mind of the villager, who might be easily led to refuse further treatment of his animals after the experience. The smaller dose was therefore deemed adequate, to be repeated after an interval of a few days to a week at longest.

The records of the Department show that the following quantities of sterile trypanblue have hitherto been issued annually from the headquarters laboratory at Nagpur :—

	Cubic centimetres
1922-23	9,840
1923-24	72,420
1924-25	142,600
1925-26	139,210
1926-27	256,675

3. *Mode of administration.* When the drug was first issued, it was administered by subcutaneous injection. Steps were soon taken, however, to train the subordinate staff in the proper method of administering it by intravenous injection. With the adoption of the requisite precautions regarding sterility at the time of injection, the formation of abscesses became increasingly rare. When abscesses

did occur, they could nearly always be traced to lack of cleanliness on the part of the operator and in the dispensaries, which, on inspection, were found to be below average in the matter of "Care of Drugs and Instruments," to quote one of the headings in the inspection returns.

While the possibilities of the drug were being explored during the first year it was on trial, some interesting practical information was obtained upon the subcutaneous injection of trypanblue into dogs. Wallis HOARE (*System of Veterinary Medicine*, Vol. I, page 1032) recites the African experience that injection in this way is attended with untoward consequences in dogs as "there was a great tendency to abscess formation if aseptic precautions were not taken." The experience we gained in the course of our work was similar, so long as the injections were made into the inner, flat surface of the thigh. The proneness to abscess formation at this site was thought to be associated with the likelihood of the animals conveying infection from their anal and genital region to the seat of injection by repeated licking of one part and then the other, and so various other parts of the body surface were tried for inoculation. It was found that abscess formation became extremely rare when the sites chosen were either subcutaneously on the side of the neck, or intramuscularly by deep injection into the gluteal muscles. In fact, abscess formation then was no more common than in the larger animals after inoculation of the drug, and when it did occur, it could be traced to the neglect of elementary precautions in the observance of sterility of the kind already mentioned.

At the present time, the method of administering the drug is entirely by intravenous injection, except at a few outlying stations where the Veterinary Assistant Surgeons have not yet been trained in the proper technique. In the larger animals, the jugular vein is selected for injection, and in dogs the external saphena vein.

4. *Clinical results.* After an extensive trial had been given to the treatment, over five years, the Veterinary Inspectors and Assistant Surgeons were requested to furnish detailed reports upon the results achieved by them in the course of their experience. Unfortunately, it is not practicable to publish in this short article their communications *in extenso*, and so striking records, numbering over a hundred have perforce to be omitted. It is believed, however, that the efficacy of the treatment is fairly summarised in the following excerpts from the reports. In general, the reports dealt with the treatment from two standpoints, namely, first, as a cure for acute piroplasmosis, and, secondly, as a restorative in chronic affections manifested by symptoms of debility.

(*a*) "Its general value as a tonic is undoubtedly a great one. Many unthrifty animals put on condition after one or two injections of trypanblue and its use is getting very popular with cattle owners. In milking cows, injections result in a better yield of milk and the quality and quantity of the butter is increased considerably. I have found it very useful in cases of chronic skin affections in dogs."

(*b*) " Its value as a general tonic is unparalleled. There have been many instances in which animals have shown wonderful improvement in condition after one or two injections."

(*c*) " In acute cases an injection of trypanblue almost immediately brings down the temperature and clears the blood of piroplasms. Even if the blood is still free after seven days, a second dose should be given. The present dosage is sufficient. In chronic cases, at least three doses are necessary at intervals of a week, or earlier if the mucous membranes show no blue staining. As a general tonic, it is much more useful than iron, arsenic, etc. Milch animals, which give an inferior quality of milk in spite of good food and tonics, yield a large quantity and a better quality of milk after injection. In two recent cases, a cow and a she-buffalo which had dried up almost entirely owing to unknown causes started to give milk after the first injection. I am of opinion that for all debility cases trypanblue should be adopted as a routine treatment whether parasites are found in the blood or not."

(*d*) " In acute cases of piroplasmosis early treatment with trypanblue has been found efficacious in over 95 per cent of cases. I have treated many cases of indolent ulcer, which defied all ordinary treatment, by means of trypanblue injections combined with external dressings of an ordinary kind. Other chronic diseases of a constitutional nature such as recurrent colic and tympanites showed rapid resolution when the dye was used in conjunction with ordinary medicaments which by themselves had failed to effect resolution."

An inspector reports that although he obtained excellent results with the drug in indigenous breeds of cattle, he failed to obtain results that were equally striking in animals that were either imported stock or the progeny of imported stock mated with the local cattle.

5. *Action on Foot-and-Mouth Disease.* In 1923, injections of the drug were tried upon animals in the scene of outbreaks of this disease. It was found that when the drug was administered during an early stage of the disease, while the animal was exhibiting an acute febrile reaction to infection, rapid improvement took place, and the length of time that elapsed between the first appearance of symptoms and eventual complete resolution was curtailed by a half in the treated animals. The drug, however, was found to have no prophylactic action. It is of interest to note that DAVIDSON (*Veterinary Journal*, 1924, Feb.) has reported similar results with the use of the drug in Hong Kong.

6. *General Remarks.* From these observations, it may be inferred that the utility of trypanblue in the treatment of piroplasmosis, of the acute and chronic types, has received confirmation in practice in the Central Provinces. The results that may be expected from its use are in no wise surpassed by those reported to have

been obtained in other countries. Further, in the numerous cases of chronic debility, slowly healing wounds, and other local manifestations of a probable systematic disturbance, the exhibition of the drug may be followed by rapid clinical improvement, whether piroplasms are readily demonstrable by microscopic examination in the peripheral blood or not. The utility of the drug in the treatment of animals affected with foot-and-mouth disease, in its early stages, has also been confirmed.

Intramine.

In 1922, the writer's attention was attracted by Mr. A. G. Dix, I. E. S., to a report upon a new basic aniline dye prepared by Dr. H. H. Hodgson, College of Technology, Huddersfield; this dye appeared to be allied to the intramine referred to by MacDonagh in his Hunterian Oration (1916), entitled "Links in a Chain of Research on Syphilis." At the author's request, Dr. Hodgson kindly despatched to him samples of certain 00dithio-anilines for trial. Some of these compounds were soluble only in solutions of sodium thiosulphate or caustic soda, but later samples were received that were soluble in water alone. The preparation known as intramine, although it is referred to here as a dye, is in reality a colourless substance, and it is administered in one per cent watery solution.

During the years 1923 and 1924, a series of experiments was carefully executed upon these drugs to test their efficacy in piroplasmosis, trypanosomiasis, and foot-and-mouth disease. It would extend beyond the limits of this short contribution to reproduce in detail the records of these experiments, which can, however, be readily furnished on request by the author for scrutiny.

The total number of animals treated in hospital for piroplasmosis was 38, namely, 6 ponies, 12 cattle, 3 buffaloes and 17 dogs. The chemical substance designated intramine was administered both subcutaneously and intravenously. Smear preparations of the blood of these animals were examined daily microscopically, and temperature readings taken. It was found that the piroplasms disappeared from the blood stream within 24 hours after administration of the drug. The blood of nearly all of these animals was examined from time to time for periods extending to two or three months, and in only two of them were there any signs of persistence or recurrence of parasitic invasion.

As the drug is colourless, it has an advantage over trypanblue in that it does not stain the mucous membranes and other tissues after injection. This characteristic is not of such consequence in India as it might be in countries like England, where the prolonged staining caused by trypanblue is considered very objectionable. The intramine preparation, however, did not seem to exercise any tonic or restorative effect, in the manner already indicated in describing the properties of trypanblue. Perhaps this defect need not be looked upon as a grave deterrent towards the use of the drug in countries like England, where, after specific destruction of the piroplasms, treatment can be readily continued by the administration of a course of

so-called tonic medicines. In India, however, the conditions of treatment differ greatly, for a skilled veterinarian has official charge of a large tract of country and finds it generally impossible to keep individual animals under prolonged observation. The dithio-aniline preparation again seemed to exert no appreciable inhibitory effect upon trypanosomes.

Action upon Foot-and-Mouth disease. The following is a brief summary of experiments carried out to determine the efficacy of the drug in the treatment of this disease.

Experiment No. 1. Three calves were used, two of which were injected intravenously with 30 c.c. of a solution of intramine, in a one-third dilution of the usual one per cent. strength, while the third was allowed to remain untreated as a control. All three calves were then artificially infected, by feeding them on grass heavily contaminated with saliva and discharges from the foot lesions of animals naturally affected with the disease; in addition, the gums were scarified and infective saliva applied to them. The two calves that were injected in the meantime with intramine showed very considerable resistance to infection: one calf remained normal in appearance throughout the period of observation, while the other calf showed on the eighth day a rise in temperature (103·6°F and 103·8°F), which, however, subsided to normal on the following day, and no outwardly visible symptoms developed. The control calf showed a rise in temperature amounting to 104·6°F on the eighth day, and shortly afterwards on the same day there appeared on the upper lips and gums erythematous spots, some of which developed into ulcers by the 11th day and were considered to be sufficiently characteristic of typical foot-and-mouth disease lesions.

Experiment No. 2. This experiment was carried out on a herd of 45 bullocks, cows and calves belonging to the Nagpur Jail. On April 26th, foot-and-mouth disease appeared in this herd, and on the following day six bullocks were injected intravenously with 30 c.c. of the one per cent. intramine solution. On April 28th, that is, 48 hours after the first appearance of the disease in the herd, one of these bullocks developed a foot lesion, with a rise of temperature of 104°F. On May 3rd, the remaining five bullocks were given a second injection; on the same day, two fresh calves and three bullocks were injected with the drug and introduced into the infected herd. None of these ten treated animals showed subsequently any febrile disturbance or symptoms of foot-and-mouth disease: they were the only animals in the jail herd that escaped clinical affection.

Experiment No. 3. This experiment was undertaken in the field, under the supervision of Mr. R. V. Pillai, G.B.V.C., on a large herd of cattle in which foot-and-mouth disease had already appeared. It was found that the injection of intramine cut short the course of the disease to an even more striking degree than had been observed by DAVIDSON and in our own experience with the use of trypanblue.

Foot-and-mouth disease assumes a much less virulent form among indigenous cattle in India than it often does among European herds. It was considered

therefore that the drug was worthy of trial upon the more virulent European disease, and while he was on leave in England, the author approached the late Sir Stewart STOCKMAN with the object of putting him in touch with Dr. HODGSON to get samples of the dithio-aniline preparations to test in actual outbreaks. It was explained to the author, however, that any attempt at therapeutic treatment was contrary to the declared policy of the Ministry of Agriculture, and so the tests could not be carried out. It is believed, however, that it would be worthwhile for British practitioners to test the preparations upon clinical cases of red-water, especially in view of the advantage they possess in not giving rise to discolouration of the tissues. The author feels sure that Dr. HODGSON would be prepared to put at their disposal any material they required for the purpose.

From the economic standpoint, the employment of intramine has the considerable merit that the actual cost of the drug is relatively negligible. The dithio-aniline compound, intramine, is a bye-product in preparation of other aniline derivatives, and it can be sold now at a price of about one shilling a pound. Three grammes are sufficient to make 300 c.c. of solution for intravenous injection, and the quantity of solution required for an average sized beast is 30 to 40 c.c. The actual cost of the material for one dose therefore amounts to less than one-hundreth of a penny.

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Memoirs of the Department of Agriculture in India

Nasal Granuloma of Cattle in Bihar and Orissa

(Experiments regarding mode of Infection and treatment).

BY

RAI SAHIB P. N. DAS

Assistant Director, Civil Veterinary Department in Charge of Orissa Range

AGRICULTURAL RESEARCH INSTITUTE, PUSA

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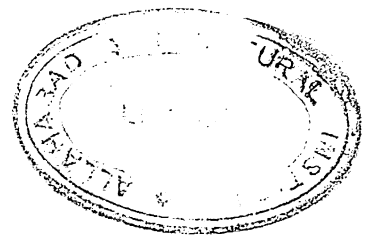
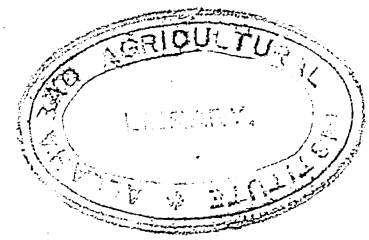

NASAL GRANULOMA OF CATTLE IN BIHAR AND ORISSA.

EXPERIMENTS REGARDING MODE OF INFECTION AND TREATMENT.

BY

RAI SAHIB P. N. DAS,

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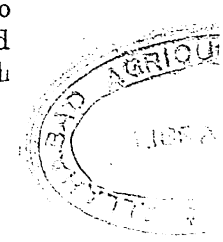
(Compiled in February 1925 and received for publication on 23rd August 1928.)

INTRODUCTION.

Nasal Granuloma appears to have existed amongst the working bullocks in certain parts of this Province for a very long time. The disease is believed to be commonly prevalent in other provinces of India too. The occurrence of the disease in the Madras Presidency was first reported by two veterinary assistant surgeons in 1919 in the third issue of the Madras Veterinary Journal, while its existence in Assam was mentioned in an official communication of the Muktesar Research Laboratory. Mention of this disease does not occur in English or continental literature, so that it would appear to be confined to the Indian peninsula. The disease generally goes by the name of "Nakhra" or "Sinsunia", *i.e.*, an affection of the nostrils. The popular idea is that the disease is an incurable one, there being considerable depreciation in the value of an affected animal owing to the difficulty of breathing interfering with work capacity.

Messrs. Krishnamurti of the Madras Veterinary College and H. Cooper of the Muktesar Institute studied the disease particularly in relation to the pathological condition of the growth on the schneiderian membrane and the causal organism responsible for the disease. The former read a very interesting article on the subject and demonstrated some specimens of the disease in the second Veterinary Conference held at Calcutta in 1923. Both these authors described a ray fungus as the causal organism akin to the kind which is responsible for actinomycosis; but the exact mode of infection, the biological character of the organism, and the period of incubation are still obscure. All forms of medical and surgical treatment had proved valueless until 1921 when the veterinary surgeon of Saidapet veterinary hospital reported having used tartar emetic with conspicuous success and was even led to regard the drug as a specific for the disease, although Mr. Krishnamurti was inclined to consider that it had no curative value. The drug has since been used with



considerable success in the treatment of a number of cases and it has even been reported that a veterinary assistant in Madras cured an advanced case with a single massive dose of tartar emetic administered intravenously. The drug would then appear to possess an undoubted curative value, although the statement that a single injection of the drug is capable of effecting a cure in the case of chronic affection without any detrimental results being produced in the patient is correct, needs confirmation.

Occurrence of Nasal Granuloma in Bihar and Orissa and application of tartar emetic in the field.

In January 1923 and again in March of the same year specimens of Nasal Granuloma were forwarded to the Imperial Institute of Veterinary Research, Muktesar, and detailed reports on pathological condition of the growths obtained. Six affected cattle were also despatched to the Institute during August 1923 in order that they might be subjected to careful investigation.

During the cold weather of 1924 the Director, Civil Veterinary Department, Bihar and Orissa, decided to have an enquiry made into the incidence of the disease in the Province and the Veterinary Inspectors of the Central Range were instructed to report the number of affected animals in their respective jurisdictions and to test the curative value of intravenous injections of tartar emetic whenever an opportunity for the application of the drug presented itself. The number of cases reported was 1,513 all appearing in an enzootic form and out of these 71 cases were treated with intravenous injections of tartar emetic, in doses ranging from 10 to 20 grains in 20 c.c. of distilled water. Treatment could not be carried out in the case of the others.

In one out of six villages in which the operation was conducted, the animals were treated by means of five injections each ; in four others, two to three injections ; wnilst in the sixth village, not more than one injection was given to each animal. The cases treated with the maximum number of injections were actually either cured or at any rate improved in condition, but those treated with fewer doses did not appear to have derived any lasting benefit. The number of deaths reported was only five. Although the immediate results of the treatment would thus appear to have been satisfactory, the actual curative value of the drug would be determined by the permanence of the therapeutic effect produced in the treated animals.

Transmission of Nasal Granuloma and treatment of the disease under experimental condition.

With a view to studying the method of infection and to ascertain the value of the treatment as expressed by the permanence of the therapeutic effect produced by it a series of experiments was conducted upon five healthy and eight diseased cattle. The experiments extended over a period of 9 months from 28th March to 23rd December 1924.

All the experimental animals were maintained as far as possible under the same conditions as obtain in the villages and were in addition allowed to graze together during the period from 1st July to 14th November 1924. During the progress of the experiments all variations in weather conditions except severe cold were experienced.

(A) *Mode of infection.*

Ordinarily, the disease is supposed to be directly transmitted from the infected to healthy animals but the possibility has also been suggested of the causal agent being harboured, in saprophytic form or otherwise, in soil, fodder or water.

In order to test these possibilities, a series of experiments was performed upon a herd of animals maintained at the Bankipur veterinary hospital composed as follows :—

Nos. 1 to 6	affected.
„ 7 to 10	unaffected.
No. 11	affected (returned as unsuitable).
„ 12	unaffected.
„ 13	affected.

The following is a brief account of the experiments carried out :—

(1) *Feeding and watering healthy and diseased animals in the same trough.*

(*a*) No. 7, aged Taylor bred cow, weight 4 maunds and 30 seers, purchased in the city. Fed and watered with :—

(i) No. 1, bullock, (affected with acute disease) from 28th March to 12th July 1924.

(ii) No. 5, bullock, from 13th July to 12th September 1924.

(iii) No. 13, bullock, from 13th September to 21st December 1924.

Result. The test animal failed to contract the infection.

(*b*) No. 8, bull-calf, 1½ years old, weight 1 maund and 30 seers, purchased in the city. Fed and watered with :—

No. 5 (affected with subacute disease) from 28th March to 13th September 1924.

As it failed to take the infection, a further attempt to set up the disease was made on the 15th September 1924, by means of an intravenous injection of 5 c.c. of emulsion of morbid material obtained from No. 13.

Result. The test animal failed to contract the disease.

(*c*) No. 12, aged bullock of medium size, brought from north bank of the Ganges (Hazipur). Fed and watered with :—

(i) No. 6, bullock, from 5th to 11th September 1924.

(ii) No. 13, bullock, from 12th to 14th September 1924.

(iii) No. 6, from 15th September to 21st December 1924.

Allowed to graze with the diseased animals on the maidan.

Result. The test animal failed to contract the disease.

(2) *Rubbing on the scarified surface of healthy nasal mucous membrane material from a diseased nasal growth.*

(*a*) *Healthy bullocks Nos. 9 and 10.*—Aged, of medium size. The former weighed 4 maunds and the latter 4½ maunds, both being brought from Hazipur (north bank of the Ganges). On 13th July 1924, the left nasal mucous membrane of bullock No. 10 was well scarified and rubbed with material obtained from a fresh diseased nasal growth in an outpatient (Case No. 550 of the Bankipur veterinary hospital). The patient represented a typical case of nasal granuloma and was brought from a village about 8 miles from the city.

The material was ground into a mortar to the consistency of thick paste and was then thoroughly rubbed into the scarified healthy mucous membrane.

The same operation was repeated on the 15th September 1924 with fresh material obtained from No. 13, also a typical case of nasal granuloma. The material was obtained by scraping the affected mucous membrane with a scoop and collected in a petri dish.

Operations repeated after six days.

Result. The test animals failed to contract the disease.

(*b*) On the 12th November 1924, another specimen of diseased growth obtained from an untreated case of typical nasal granuloma from village Nargoda in Dinapur Subdivision and the material rubbed on the scarified mucous membranes of the healthy animals Nos. 7 and 12.

Result. The test animals failed to contract the disease.

(3) *Subcutaneous injection on both sides of nasal peak of healthy animal with an emulsion of nasal growth.*

On the 15th September 1924, fresh nasal growth obtained from case No. 13 was ground down in normal salt solution and 30 c.c. of the emulsion was injected into healthy bullock No. 12 under the skin on both sides of the nasal peak.

Result. The test animal failed to contract the disease.

(4) *Submucous injection of healthy nasal mucous membrane with infected material.*

On the 12th November 1924, about 2 c.c. of an emulsion made from the fresh material from an untreated typical case of nasal granuloma obtained from village Nargoda (Dinapur Subdivision) was injected under the submucous membrane of the left nostril of healthy bullocks Nos. 9 and 10 admitted on the 12th July 1924.

Result. The test animals failed to contract the disease.

(5) *Intravenous injection of healthy animal with infected material.*

On the 15th September 1924, a thin emulsion in normal saline solution was prepared from the material obtained from case No. 13. 5 c.c. of this was injected intravenously into healthy bull calf No. 8 admitted on 28th March 1924.

Result. The test animal failed to contract the disease.

(6) *Application of " nose strings " used on diseased animals.*

On the 9th August 1924, two nose strings used on two typical cases were obtained from the Khajpura village, about 4 miles from the Veterinary Hospital, and were inserted, while still moist, into the nose of healthy animals Nos. 9 and 10.

The nose strings after insertion were occasionally pulled up and down until the nostrils bled. This process was continued for about a week.

On the 25th August 1924, the nose string of No. 11 diseased animal was interchanged with that of No. 9 healthy bullock and the process of pulling it up and down continued for three days.

Result. The test animals failed to contract the disease.

(B) *Curative treatment with potassium iodide and tartar emetic.*

Treatment was applied in the case of 7 diseased animals as follows :—

(1) *Intravenous injection of potassium iodide at intervals of 7 days.*

(*a*) No. 1, an aged bullock, weight 5½ maunds, bought at Bhagbatipur, about 8 miles from the hospital.

When admitted, it snored even while resting and showed symptoms of severe asphyxiation when it was made to work. An examination of the nostrils revealed the presence of ulcerating growths which bled on the slightest manipulation. The animal was believed to have been affected for about 6 months.

(*b*) No. 6, an aged bullock purchased from the same village ; weight 6½ maunds, condition fair.

Snoring was not marked but examination of nostrils revealed ulcerating growths.

Treatment. The drug was dissolved in distilled water in the proportion of 10 grains to an ounce and administered intravenously at intervals of 7 days, at the rate of 10 grains in the case of No. 1 and 5 grains in the case of No. 6. The treatment commenced on 28th March and terminated on 9th July 1924, so that No. 1 received a total of 140 grains and No. 6, 70 grains of potassium iodide.

Result. No improvement up to 13th July 1924.

(2) *Intravenous injection of tartar emetic at intervals of two days.*

No. 5, a six-year old bullock of medium size ; weight 6 maunds, purchased from the village Bhagbatipur on 27th March 1924 and admitted to the hospital the same day.

It showed thick ulcerating granular growths in both the nostrils, markedly narrowing the nasal passages, with a thick whitish discharge. The condition of the animal was fair.

Treatment. The animal received 170 grains of tartar emetic in 34 injections at the above intervals between the 28th March and the 12th July 1924, the dose used being 5 grains of tartar emetic in 30 c.c. of distilled water.

Result. The animal showed no symptoms of reaction to the drug. It was cured and discharged on the 20th October 1924, and no recurrence of the disease was reported up to the date of the compilation of the paper.

(3) *Intravenous injection of tartar emetic at intervals of 7 days.*

No. 3, a grey bullock, 5 years old, of medium size ; weight 4 maunds 10 seers, purchased from the same village and admitted to the hospital on 27th March 1924.

This animal was suffering from a subacute type of the disease. Snoring not very marked. Growth not prominent. The condition of the animal was fair.

Treatment. 140 grains of tartar emetic were given in 14 injections at intervals of 7 days, the dose used being 10 grains of tartar emetic in 20 c.c. of distilled water.

Result. The animal showed no symptoms of reaction to the drug. It was cured and signs of recurrence were not noticed up to 22nd September 1924 when it was sold to the Patna Administration Committee. No recurrence of the disease has been reported up to the date of the compilation of the paper.

(4) *Intravenous injection of tartar emetic at intervals of 11 days.*

No. 2, a brown, aged bullock of medium size ; weight 6 maunds and 10 seers, purchased from the same village and admitted on 27th March 1924.

This animal was known to be suffering from the disease for about 2 years. Breathing was very marked on admission.

Treatment. It received 108 grains of tartar emetic in 9 injections up to 1st July 1924 at the rate of 12 grains of tartar emetic in 30 c.c. of distilled water at intervals of 11 days. The treatment was discontinued after the 9th injection on 1st July 1924 by which date all the visible symptoms of the disease had disappeared completely. On the 1st September 1924, *i.e.*, two months after the last injection, it was noticed that the nasal mucous membrane had become slightly rough and superficially ulcerated. The animal was kept under observation up to 3rd October 1924 and no further aggravation of the symptoms was reported. As the administration of two additional doses at an interval of 4 days was not followed by any marked improvement, the drug was given every alternate day in doses of 10 grains dissolved in 20 c.c. of distilled water. In this manner it received 90 grains of the drug in 9 doses up to 4th December 1924 when it was discharged as cured.

(5) *Intravenous injection of tartar emetic at intervals of 14 days.*

No. 4, an aged bullock of medium size ; weight 4 maunds, purchased along with other diseased animals from the same village and admitted on 27th March 1924.

The animal appeared to have been suffering from a subacute form of nasal granuloma although the duration of the disease could not be ascertained.

Treatment. The animal was given 80 grains of tartar emetic in 8 doses at intervals of 14 days from 28th March to 11th July 1924. There was no recurrence of the growth up to 3rd October 1924 when it was sold to the Patna Administration Committee.

Treatment adopted in the case of three bullocks two of which were first treated with potassium iodide and the third was used as a control.

Case No. 1, which received 140 grains of potassium iodide, having shown no improvement, was given 15½ grains of tartar emetic in 50 c.c. of distilled water intravenously. The animal died the same night.

Case No. 6, which received 70 grains of potassium iodide in 14 injections, having shown no improvement, was given 105½ grains of tartar emetic in 10 injections, the first dose being 15½ grains in 50 c.c. of distilled water and subsequent 10 grain-doses at intervals of 7 days. The animal showed all signs of recovery after the last injection.

Case No. 13. This animal which was admitted on 12th September 1924 was used as a control and it also provided material for experiments with effect from 30th November 1924. It was treated by means of tartar emetic administered in 10 grain-doses, in 20 c.c. of distilled water, at 4 days' intervals ; it thus received 90 grains of the drug when it was discharged as cured. A large, hard and painful swelling was noticed after the last injection. It later developed into an abscess but it eventually healed without giving much trouble.

Summary of Results.

(*a*) *Experiments on transmission of nasal granuloma.*

(1) Three clean cattle were fed and watered in company of diseased animals.

(2) Two clean cattle had their scarified mucous membranes rubbed at different times with material obtained from fresh nasal growths, the material being derived from three different sources.

(3) One bullock was injected subcutaneously on both sides of the nasal peak with 30 c.c. of an emulsion prepared from a nasal growth.

(4) Two clean cattle were given submucous injections of an emulsion made from an untreated case of typical nasal granuloma.

(5) One healthy bull-calf was given intravenous injection of an emulsion prepared from diseased material.

(6) Two healthy bullocks (Nos. 9 and 10) had strings from diseased animals put on their noses and the strings were occasionally pulled up and down until the nostrils bled.

The test animals in all cases failed to contract infection.

(*b*) *Treatment with potassium iodide and tartar emetic.*

Altogether 7 cattle were treated and these resolve themselves into three categories :—

(i) Cases Nos. 1 and 6 were first injected with 10 and 5-grain doses respectively of potassium iodide intravenously at intervals of 7 days. The first animal received 140 grains and the second 70 grains of the drug in 104 days, but neither showed improvement. Both the animals were then given tartar emetic intravenously. Case No. 1 died after receiving the first injection of 15½ grains in 50 c.c. of distilled water. Case No. 6 was discharged as cured after 105½ grains of tartar emetic

were given in ten injections, the first injection being 15½ grains of tartar emetic in 50 c.c. of distilled water.

(ii) Cases Nos. 2, 3, 4 and 5 were regularly treated with varying doses of tartar emetic at different intervals. The first animal (case No. 2) received 108 grains of tartar emetic in 9 injections and subsequently received 90 grains in 9 injections. No. 3 received 140 grains of tartar emetic in 14 injections. No. 4 received 80 grains in 8 injections and No. 5, 170 grains in 34 injections. The best results were observed in the case of No. 4 which made a complete recovery after it had received only a few injections.

(iii) Case No. 13 was first used as a control but was afterwards treated with intravenous injections of tartar emetic administered in 10 grain doses at intervals of 4 days. The animal recovered after receiving 90 grains.

Conclusion.

Experience in the field and the results of the experiments described above indicate that under ordinary conditions nasal granuloma cannot be transmitted from animal to animal or through the agencies of soil, fodder or water.

The infection cannot also apparently be transmitted by subcutaneous, submucous or intravenous injection of diseased material.

The disease does not also appear to be capable of transmission through the nose strings of affected animals ; at any rate the experiment failed to demonstrate such a possibility.

Treatment with potassium iodide is not effective.

For a medium-sized animal, the best results may be expected from injections of 10 grains of tartar emetic in 20 c.c. of distilled water administered at intervals of 4 days.

Massive doses do not appear to have any curative effect. A sound plan would appear to be to repeat the injections in small doses (10 to 12 grains) and at less than 4 days' intervals. When smaller doses are employed, the interval may be reduced to one day.

The administration of the drug by the subcutaneous route cannot be recommended, as such a procedure results in the formation of large and painful local swelling lasting for many days.

Note.—J. T. Edwards, D.Sc., M.R.C.V.S., Director, Imperial Institute of Veterinary Research, Muktesar, in commenting upon this article has made some valuable observations regarding treatment with potassium iodide and tartar emetic which are quoted below for general information. I believe this suggestion for the use of tartar emetic will prove to be the most practical as well as the safest method of treatment for adoption in the field.

" It is curious to note that potassium iodide exerts no beneficial effect upon the condition, especially as this drug has a pronounced effect upon the clinically similar condition, actinomycosis.

It may be that this is evidence that the condition is not in reality a streptothricosis, in spite of the fact that "granules" apparently indistinguishable from those of actinomycosis are discoverable in the lesions.

I note that one of your bullocks succumbed after the administration of 15½ grains of tartar emetic in 50 c.c. of water intravenously, and that the dose you recommend varies from 10 to 12 grains in 20 c.c. of water.

We have found here (Muktesar) that cattle tolerate doses of 5 c. c. of a 3 per cent. solution per 100 lb. body weight quite readily, although when the blood is rich in trypanosomes the administration of this dosage may be followed by accidents, due, it seems, to sudden destruction of the trypanosomes and occlusion of the capillaries. For the larger animals in your experiments, averaging 500 lb. body weight, our dosage would therefore be 0·75 gram (or about 12 grains), which is just about the rate you recommend for treatment. We have found in addition that this dosage can be given daily for a number of days (10 or perhaps more). It is not safe to increase this dosage although some animals will tolerate twice the rate (*i.e.*, 10 c.c. per 100 lb.), for three days.

In distributing the drug for treatment I think it would be wise to put it up in freshly prepared solutions containing a certain percentage of tartar emetic (say 3 per cent.) and instruct your staff to give it at a certain rate per unit body weight; otherwise, you may get accidents from overdosage.

Also, I believe in this treatment there is no question of a *dosis sterilisans magna*, *i.e.*, sterilisation by the administration of a single large dose, but rather a therapeutic effect caused by the cumulative action of the drug administered in suitably large doses repeated at suitable intervals. We know that tartar emetic is excreted, or, at least, its action is not discernible in the blood stream (surra experiments) after an interval of 3 days. I see no reason, therefore, why the drug should not be administered at very short intervals with the object of curtailing—if the end results are dependent upon the total amount of the drug administered—the period of treatment. Again, according to this view, the initial doses should be small, to test the idiosyncrasy or the susceptibility of the animal to the drug.

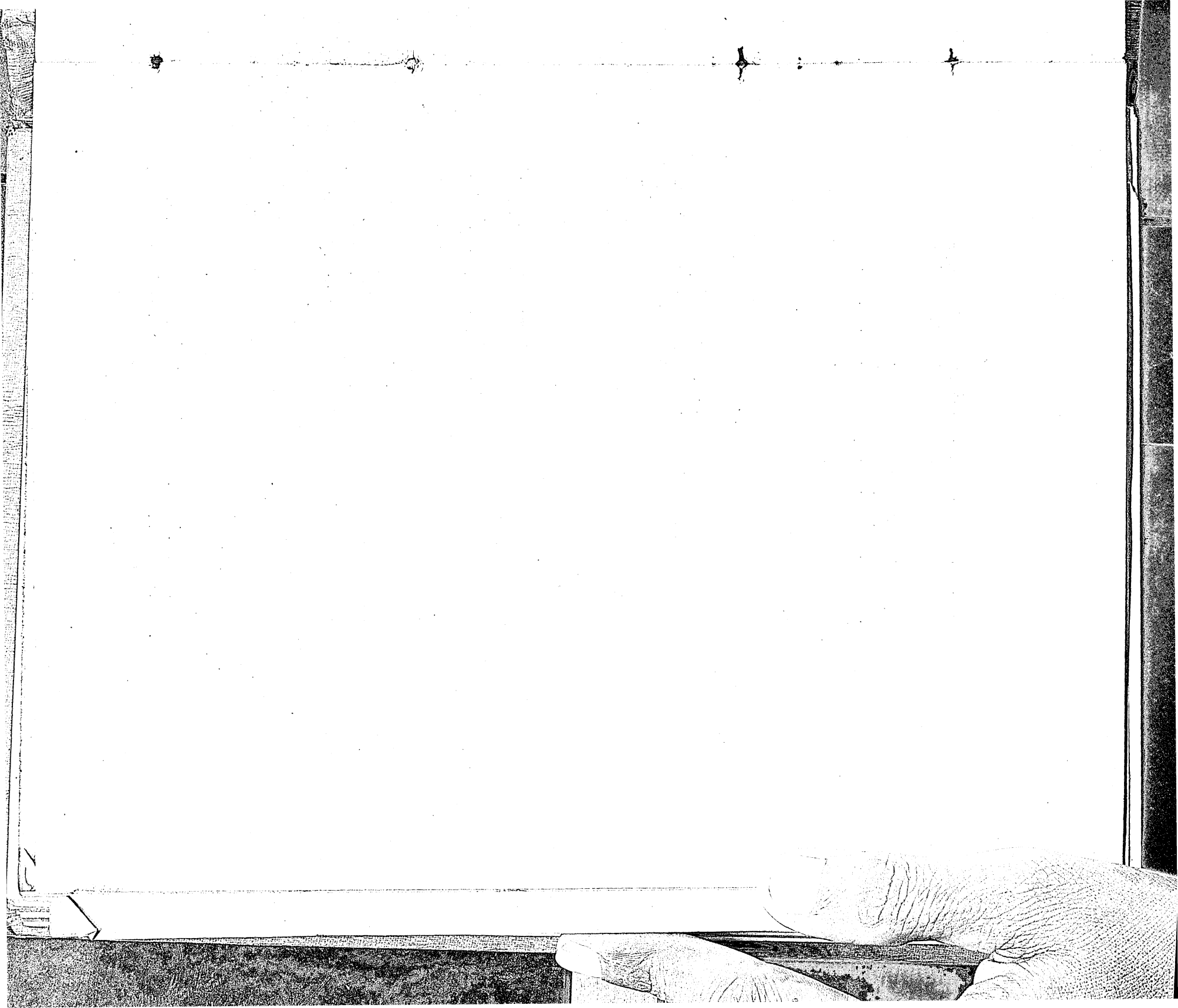
It is of interest to compare the mode of treatment adopted in human schistosomiasis (bilharziasis) with tartar emetic (see Byam and Archibald, the Practice of Medicine in the Tropics, Vol. III). If an analogous system were adopted for a bullock of 500 lb. body weight the system would be :—

A
- First day . . . . . 2 grains
- Second day . . . . . 4 „
- Third day . . . . . 6 „
- Fourth day . . . . . 8 „
- Fifth day . . . . . 12 „

(If preceding dosages are tolerated) 6th, 7th and 8th days same dosages as on the 5th

B Allow one clear week to elapse without treatment and then repeat the 5th day treatment for three successive days.

C Send the bullock now away, to be returned for inspection in a month's time, and if the lesions have not disappeared, repeat the treatment given under B."



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